MEDICAL LIBRARY

NOV 8 1949

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY OCTOBER 22 1949

TABLE OF CONTENTS

Artificial Kidney
GORDON MURRAY, M.D., F.R.C.S., EDMUND DELORME, M.D., F.R.C.S.Can., and NEWELL THOMAS 887

Malaria.—II N. HAMILTON FAIRLEY, C.B.E., M.D., F.R.C.P., F.R.S. 891

Natural History of Asthma ELSIE O. WILLIAMS, M.B., D.P.H., and G. E. O. WILLIAMS, M.D., M.R.C.P. .. 897

Antihistamines in Bronchial Asthma HERBERT HERXHEIMER, L.R.C.P.&S.Ed. 901

Case of Toxoplasmosis
A. B. NUTT, F.R.C.S., TREVOR WRIGHT, M.D., J. H. BOWIE, M.B., and C. P. BEATTIE, M.B. 905

Chloramphenicol in Typhoid Fever
J. C. PATEL, M.D., D. D. BANKER, M.D., and C. J. MODI, M.B., B.S. 908

Pneumococcal Meningitis Treated by Replacement of C.S.F. with Penicillin
ALASTAIR ARNAUD REID, M.B., B.S. 910

MEDICAL MEMORANDA

Chloramphenicol in Typhoid Fever. W. LOMAX, M.D., D.P.H. 911
Staphylococcal Portal Pyaemia. CHRISTOPHER STRANG, M.B., M.R.C.P. 912

GENERAL ARTICLES AND NEWS

The Acute Ear. W. M. MOLLISON, F.R.C.S. 923
FUNCTIONAL DIFFERENTIATION IN MAMMARY TUMOURS 925
Heparin Administration by Polythene Tubing. W. A. L. MACFADYEN, M.D. 925
UNIVERSITIES AND COLLEGES 935
MEDICAL NEWS 937
BIRTHS, MARRIAGES, AND DEATHS 939
QUESTIONS AND COMMENTS 939

REVIEWS

Practice of Ophthalmology 913
Textbook of Haematology 913
The Technique of Transfusion 913
Radiologist and Clinician 914
Hypnosis 914
Advances in Tuberculosis 914
Morgagni's Syndrome 915
Books Received 915

OBITUARY

James Kyle, M.R.C.S. 933
J. McA. Ramsay, L.R.C.P.Ed. 933
J. P. Raban, M.R.C.S. 934
K. S. Wise, M.B. 934

Epidemiology Section 936

LEADING ARTICLES

Fresh Light on Malaria 916
Tuberculosis in England and Scotland .. 917
Chemotherapeutic Treatment of Typhoid 918

ANNOTATIONS

The Artificial Kidney 920
Asthma 921
Insulin Requirements 922
WMA 922

MEDICO-LEGAL

Overdose of Nitrous Oxide 934

REPORTS OF SOCIETIES

ROYAL SOCIETY OF MEDICINE: Progress in Ophthalmology 926

SUPPLEMENT

World Medical Association 175
Health Service.—HEALTH CENTRES—HOSPITAL DENTAL STAFF—DISCIPLINE AND PUBLICITY—OCCASIONAL ATTENDANCE ON ARMY PERSONNEL 181
WMA: COUNCIL DINNER 181
QUESTIONS ANSWERED 182
HEARD AT HEADQUARTERS 183
GENERAL MEDICAL COUNCIL 183
SCOTTISH COMMITTEE 184
CORRESPONDENCE 184
B.M.A. LIBRARY 186
H.M. FORCES APPOINTMENTS 187
ASSOCIATION NOTICES 187

CORRESPONDENCE

Progress in Obstetrics. S. BENDER, M.D.; ANDREW M. CLAYE, F.R.C.S.; W. RADCLIFFE, M.B. 927
A Year of N.H.S. E. D. IRVINE, M.D. .. 928
The Innocence of Deans. GEOFFREY BOURNE, M.D. 928
Modern Trends in Radiology. F. D. BEDDARD, M.B.; S. COCHRANE SHANKS, M.D. 928
Vitamin Deprivation. Z. A. LEITNER, M.D. 929
Infant Vaccination. C. KILLICK MILLARD, M.D. 929
Malignant Tertian Malaria. P. ROSS, M.B. 930
Poliomyelitis. R. HARRIS, M.B. 930
Poliomyelitis Vaccination. W. P. SWEETNAM, M.D. 930
Lead Nipple Shields. R. G. HOWAT, M.B.; JOAN S. BLACKSELL 931
Congenital Pyloric Stenosis. R. MCLAREN TODD, M.D. 931
Symptoms of Psychoneurosis. F. A. RICHARDS, M.D. 931
Tetraethylthiuramdisulphide in the Treatment of Alcoholics. J. N. P. MOORE, M.D. 932
Treatment of Varicose Veins. H. M. HANSCHELL, M.R.C.S. 932
Serous Fluid in Wounds. S. DE C. BARCLAY, F.R.C.S. 932
Streptomycin in General Practice. B. COUTS, M.D. 933
Points from Letters 933

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON, W.C.1

No. 4633, WEEKLY, PRICE 1/6

Copyright

REGISTERED AS A NEWSPAPER

Against exhaustion

The energising and therapeutic effect of glucose is available in a most acceptable form in LUCOZADE.

Whereas ordinary glucose preparations may have a sickly and even nauseating effect on the palate, LUCOZADE is remarkably refreshing. Once tasted—it is never refused.

This pleasing characteristic is of the greatest value in treating cases of shock, physical exhaustion and other conditions requiring glucose ingestion.

An improved form of glucose therapy

(Containing Dextrose, Maltose, and Dextrin in solution equivalent to 23% w/v Liquid Glucose B.P.).

LUCOZADE

LUCOZADE LTD., GT. WEST RD., BRENTFORD, MIDDX.

M.17

THE REITH LECTURES, 1949

broadcast by

ROBERT BIRLEY

Headmaster of Eton, and formerly Educational Adviser to the British Military Governor in Germany

"Britain in Europe: Reflections on the Development of a European Society"

will be published in

The Listener

October 27.—"The Problem of Patriotism."
November 3.—"The Meeting of Britain and Europe."
November 10.—"Changes in Education and the Problem of a Common Language."
November 17.—"Britain's Contribution to a European Society."

A BBC Publication. 3d. every Thursday

From single-cell selection to large-scale production

D.C.L. VITAMIN B_1 YEAST

is subjected to the strictest biological and chemical control. The special yeast contains approximately:

Vitamin B_1	300 International Units per gram. (300 micrograms)
Riboflavin	50 micrograms per gram.
Nicotinic Acid	250-350 micrograms per gram.
Vitamin B_6 (Pyridoxin)	25-50 micrograms per gram.

(3 D.C.L. Tablets equal 1 gram)

Members of the Medical Profession are invited to write for full particulars and a trial supply.

THE DISTILLERS COMPANY LTD., EDINBURGH

Local Anaesthesia at its best

KEROCAIN

PROCAINE HYDROCHLORIDE KERFOOT

Procaine Hydrochloride in an exceptionally pure and reliable form, conforming to standards considerably more exacting than those of the British Pharmacopoeia. Prepared under ideal conditions and stringent analytical control.

Leaflet indicating the various preparations available on request.

KERFOOT

THOMAS KERFOOT & Co. Ltd.
Vale of Bardsley Lancashire

KG 39

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 22 1949

ARTIFICIAL KIDNEY*

BY

GORDON MURRAY, M.D., F.R.C.S., F.R.C.S.Can.

EDMUND DELORME, M.D., F.R.C.S.Can.

AND

NEWELL THOMAS

Toronto, Canada

In ancient times it was thought that the kidneys were linked closely with the temperament of the individual, and physicians of old practised largely on physic and examination of the urine. With modern pathology, much more has been learned about the kidneys in many respects, but their detailed function is still a mystery.

Our interest in an artificial kidney came only as a sideline to the work being done with heparin, and fundamentally a good anticoagulant is paramount when blood is to be circulated through any system of artificial tubes.

There were other reasons which made such an investigation more or less logical. The ever-present patient with anuria, for whom so little could be done unless the kidneys themselves decided to go to work, also offered a real challenge. The persistence of anuria in a patient who may look and feel well induces in the doctor in charge a series of changing moods ending in desperation and an admission of helplessness from ignorance of the disease of uraemia, its cause, how it acts, and its cure.

With heparin as an anticoagulant, attempts were made to clear the blood stream of toxic substances by transplantation of a kidney from one animal to another and from one species to another. This work was done in 1933–5 with moderate success (Murray, Delorme, and Thomas, 1947). The objective in this present investigation was to produce similar effects by preventing a patient from dying of acute toxaemia in such conditions as acute mercury and phenol poisoning, in the toxaemias of acute infections such as nephritis or pneumonia, etc., with oliguria or anuria, as well as in acute anurias following blood transfusions, crush, excessive sulpha-drug administration, eclampsia and toxaemia of pregnancy, severe skin burns, induced abortions, acute injury to ureters and kidneys from calculus obstructions, reflex or otherwise, or following operation. This thesis is supported by Trueta's (1947) work, in which it was shown that the cortex of the kidney may be put out of action by various reflex or other means, and that it may regain its function provided the patient survives long enough.

It therefore seemed possible, if the patient could be protected from death from toxaemia in such conditions, that after a time a number of the kidneys affected might recover enough to resume function, and such has been the case in several instances.

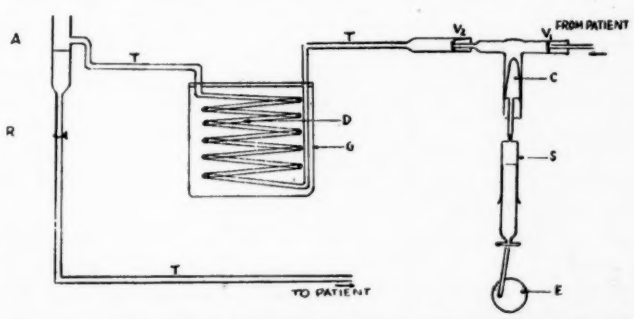
It was with satisfaction, therefore, that experimental results to justify this thesis were noted and also that clinical evidence has supported the claim. Also, it has been demonstrated repeatedly that the apparatus works smoothly for long periods, and that it performs the functions for which it was developed.

Many workers, including Abel, Rowntree, and Turner (1913, 1914), Thalhimer (1938), and numerous others, have embarked on similar investigations, but the work has not to our knowledge been developed to a point where it was a proved effective clinical method of treatment. The one exception is that of Kolff and Van Noordwijk (1946), in Holland. We were not aware of their investigations, and not until after the war did we hear of their results. Their excellent monograph gives evidence of the treatment of an extensive series of patients, with some good clinical results. Apparently our efforts have been carried on simultaneously, and they were quite independent. It was interesting, therefore, to compare the methods and the material used, and to note the different avenues followed, which evidently converged fairly closely towards the same goal of end-results.

Development of the Apparatus

The principles of our artificial kidney are: (1) a dialysing membrane which is selective in allowing the passage of some substances and not of others from the blood stream—namely, non-protein nitrogen and other toxic substances; (2) a method of circulating the blood through this extrinsic system; (3) protection from removal of necessary substances from the blood stream.

It was not until very extensive and arduous trials and experiments had been made that we finally arrived at the present set-up (see Diagram), which works satisfactorily both experimentally and in clinical patients.



Schematic diagram of artificial kidney (not drawn to scale). V_1 and V_2 = valves. C = condom. S = syringe. E = eccentric. T = rubber tubing. A = air trap. R = inlet control. D = dialysing membrane. G = Bath jar.

*Based on the Alexander Simpson-Smith Lecture delivered at the Hospital for Sick Children, Great Ormond Street, on July 11 by Dr. Gordon Murray.

The following is a summary of some of the series of events which led to the development of the apparatus and of what might be termed the evolution of this instrument.

1. The first method was the circulation of arterial blood with return through the venous side through several coils of cellulose acetate tubing (sausage-casing) bathed in warm tap-water. This tubing was 1 in. (2.5 cm.) in diameter and presented the primary disadvantage of the volume/surface-area ratio. Also, the size of the tubing allowed escape of too much of the animal's blood before there was sufficient return, if a reasonable length of it was used. In this way the animal really had haemorrhage into the tubing. Filling this with blood beforehand overcame the difficulty.

2. Later on, with considerable effort, tubing ½-in. (1.25 cm.) in diameter was obtained, with somewhat better results. Then ¼-in. (0.6-cm.) tubing was obtained from the Visking Corporation, of Chicago, and this gave fairly satisfactory results.

3. With sufficiently long sections of this tubing *in vitro* we were able to demonstrate that there was some passage of N.P.N. substances through this membrane and that the larger protein molecules did not pass (Chart 1).

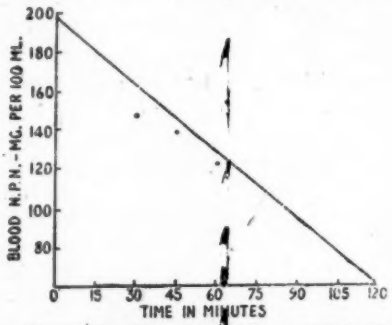


Chart 1.—Showing dialysis of N.P.N. from human blood *in vitro*. 2.3 g. of N.P.N. was removed in two hours. No proteins came through.

4. To diminish the volume of these tubes it was attempted at first to pass the tubing through a series of wire cells containing the dialysing tubes.

5. Next, concentric wire cylinders between which the tubes were partly compressed were used.

6. Then we tried a wooden reel on which the coils could be assembled fairly quickly. This did not control the volume satisfactorily.

7. Next it was decided to coil the tube round a small platform, when plastic perforated sheets were applied on each side and bolted together to compress the tubing in the coil. These were found to be unsuitable because of the bulging under the pressure of the fluid in the coil.

8. Then sheets of the plastic plates were replaced by wood, and these were found to warp.

9. The latter were replaced by aluminium-steel plates, which were bolted together with a thin definite spacing between them. This worked moderately well, but was finally discarded for

10. A vertical wire-mesh cylinder around which the tube was wound in spiral fashion and held in place by cross-pieces of wood. This method finally gave the best result with the ¼-in. tubing, and lengths up to 150 ft. (45.72 metres) of tubing could be used quite satisfactorily, giving a fairly high rate of dialysis.

Sources of the Blood for Dialysis

The next problem to be solved was that of a method of circulating the blood. Early on it was decided that using an artery as the propelling force had many disadvantages: (1) The artery could be used only once; if further attempts were to be made another vessel would be required. (2) The pressure in the system was such that there was not a satisfactory return of the venous blood by this type of pressure. Moreover, the animal tended to act as from the result of haemorrhage from the arterial bleeding.

In all these methods, of course, it is quite obvious that the animal was highly heparinized to make sure that there was no clotting or thrombosis either in the system or at the points of intake or output or in the animal itself.

It was decided to attempt to develop a method by which the blood could be taken from the venous system and then returned to it through another point. On this basis, blood was taken first from femoral veins, then from external jugular veins, but it was found that with any pump system which produced suction the vessel collapsed and acted as a valve over the tube. To overcome this difficulty a catheter of fairly large diameter was finally passed through the femoral vessels and into the inferior vena cava or into the right heart region. From this any quantity of blood could be removed by aspiration without any interference or obstruction, and it could be returned quite readily to a vein on the opposite side. This seemed to have many advantages: (1) there was no ill effect on the animal's pressure simulating haemorrhage; (2) the quantity of blood removed could be controlled accurately, which was not the case when an artery was used; (3) the venous blood, unoxygenated, was circulated through the system, and therefore more impurities were available for dialysis by this method; (4) the blood was not oxygenated, and, as well as dialysing it, it was easy to add oxygen during the circulation through the system of tubes.

Pump System

The next problem was one of providing a circulating pump system which would not damage or crush the blood corpuscles, would not produce haemolysis, would work smoothly, and would not become plugged and clotted with fibrin. At first the blood was drawn into a flask, circulated through the dialyser, and then returned to the venous system by gravity.

Next a piston syringe was used as a pump, with intake and outlet valves on glass seats, but it was early demonstrated that in spite of high heparinization the spinning of these valves and the passage of the blood through the small apertures tended to cause some collection of fibrin and to interfere with the functioning of the system. In place of this a rotary-pump effect was used, but it was only moderately satisfactory. Finally, a pump system was used whereby a rubber tambour was inflated and deflated by the action of the piston syringe attached to an electric motor. Rubber intake and outlet valves gave good results, so that a smooth circulation, without injury to blood and without clotting and deposit of fibrin or platelets, could be ensured for many hours at a stretch.

Experiments on Increasing Dialysis

Many efforts were made to increase the rate of dialysis through the membrane.

1. The best and most obvious means was by increasing the length of the tubing used. Lengths up to 35 ft. (10.67 metres) were employed quite satisfactorily, and it is possible that this length could be considerably increased with still more beneficial effect. Recently lengths of 150 ft. (45.72 metres) have been used.

2. It was thought that by attempting to reduce the atmospheric pressure surrounding the tubing an improvement in dialysis might be obtained, but the results were not very satisfactory.

3. By increasing the pressure within the dialysing tubing it was hoped that there might be some increase in the dialysis, but again this requires further study to be certain of the effect.

4. Some investigation was carried out to see if the work described by McBain and Kistler (1928, 1929, 1930, 1931) would apply under these conditions. These authors indicated that the use of 64% zinc chloride solution would stabilize the apertures in the membrane and increase the rate of dialysis. Extensive tests, covering several months, were done with this. It was our conclusion that, while there was some benefit in the rate of dialysis early in the exchange, in the final results there was not a very great difference. The difference did not seem to be great enough to justify the effort and trouble of treating the tubing, and for that reason the method was discarded and the untreated tubing was used. It was noted in our experiments

that the use of zinc chloride, with adequate washing afterwards, did not seem to produce any toxic effects in the animal.

The Dialysate

The next problem, related to the protection of the animal against the removal of substances which are necessary for life, involved a great deal of work and was the most difficult to solve.

If an animal's blood was dialysed through this instrument with a surrounding bath of tap-water it was found that within five to seven minutes the animal showed very striking clinical changes. The rate of breathing was accelerated until this became very violent. There was shock and collapse, and the animal died within a period of seven to fifteen minutes.

At this stage we were not certain whether important substances such as adrenaline, "pituitrin," insulin, heparin, and so on were being removed and whether the animals were going into shock on this account. As the chemical tests for some of these substances are exceedingly difficult and uncertain, we were not convinced by chemical analysis whether such was the case or not. However, we arrived at our final conclusions by the following methods:

During dialysis it was demonstrated that the animal had an increasing concentration of haemoglobin, and that it showed evidence of water loss. It was therefore decided to balance the dialysate surrounding the tubing with some of the normal substances in blood as indicated in Ringer's solution. It was found that by an addition serially of each one of these substances we could overcome one or other of the difficulties and could carry on a dialysis without producing these disastrous effects on the animal. When the chlorides, the calcium, the magnesium, the potassium, the sodium, the phosphate, the carbonate, and the sugar were balanced in turn these disastrous effects did not occur. In the preparation of our dialysate it was found that with the potassium left out the animal suffered ill effects and when potassium was added it was protected against these effects, and similarly with the other salts and sugar. Variations in the *p*H also caused alarming results. It was necessary to add bicarbonate to the solution so as to maintain the *p*H at a level of about 7.3. With the dialysate at this level there was no change in the blood *p*H during or following dialysis.

However, as both quantitative and qualitative tests for some of these chemicals are difficult and unreliable, we found it difficult or impossible to prove the specific effect of the lack of potassium, calcium, etc., although the experimental proof of this seemed to be adequate. Finally, a bath solution similar to that used by Seligman, Fine, and Frank (1946) was used. It contained sodium chloride, calcium chloride, magnesium chloride, potassium chloride, sodium hypophosphate, sodium bicarbonate, and dextrose in physiological amounts. This solution was well buffered, but a certain care in mixing and autoclaving was required to prevent precipitation of insoluble salts.

Transfusion of Blood

The next problem was the fact that in a smallish or medium-sized animal there was so much loss of blood into this machine before any was returned that the animal was left with saline in its circulating system and all its blood out in the apparatus. However, this was overcome by filling the machine with suitable blood for the animal. When this was done the circulation could be carried on indefinitely without ill effects.

Many of our earlier experiments were carried out *in vitro* by circulating blood and other solutions through the instrument and by placing substances in the circulating fluid which could be detected in the surrounding dialysate. Next, in a normal animal, with the circulation going, 5 g. of urea was injected and the rate or removal of this was determined. With the tendency of urea to form a closer relation in the blood of the dog, it was probably not as fair a test of dialysis as might occur in the human being, in whom the urea is separated more readily and is more easily dialysable. However, this did demonstrate the rate of removal of N.P.N. substances from a normal animal.

Uraemia in Animals

The next problem was to produce azotaemia in an animal so that the effectiveness of the apparatus could be assessed under these conditions. Bilateral nephrectomy was found to involve a number of uncontrollable factors, and the uraemia so produced was so severe and was associated with such a poor resistance in the animal that it did not lend itself to these experiments. A more gradual onset of uraemia was desirable, and was thought to be more comparable to the clinical condition in patients.

The chemical production of oliguria and anuria was investigated, but no completely selective uncomplicating poison which seemed suitable was encountered. Most of the work done on specific kidney damage involved the perfusion of the kidney by exposure and cannulization of renal vessels.

Ligation of ureters was performed on a series of animals, but sudden death, presumably from cardiac arrest, as has been described in the literature, was so frequent before dialysation could be carried out that many of the animals succumbed. Finally, an interesting method of producing uraemia was employed. The ureters were transplanted into the small bowel in the hope that there would be enough resorption of non-protein-nitrogen bodies to produce uraemia. This took place in a surprisingly short time, and high levels were reached in three or four days, associated with lethargy and diarrhoea. The animals, however, maintained their food and fluid intake, which was not the case with nephrectomized animals or in those with ligated ureters.

The study showed that blood may be circulated outside the body, and that with a reasonable length of dialysing tubing moderate amounts of N.P.N. can be removed in short periods from normal and uraemic animals, provided these animals are not moribund or in a state of severe circulatory depression. The N.P.N. level in the blood varies greatly in the above state and is a less reliable guide to the efficiency of the dialysation than is the N.P.N. measurable in the dialysate removed during the test run.

It seemed obvious from the experiments as well as from the effects on patients clinically that the level of N.P.N. substances measured in the blood gave only a poor indication of the effect of such dialysis. Obviously the N.P.N. substances in the blood stream are not produced there, but are the waste products delivered to this circulating medium from the tissues in which they are formed. This circulating medium, the blood, has the function of carrying these substances to points where they are detoxified and prepared for excretion, and finally are carried to the kidney, where they are excreted from the system. While the level of N.P.N. substances in the blood may be reduced somewhat, the essential point in treatment is to reduce these and other toxic substances in the vital centres and other fixed tissues. During many of the experiments and in the clinical runs more N.P.N. was removed than was contained in the total volume of blood in the animal and still the level in the blood stream was lowered only slightly. Thus it was obvious that there is a constant drainage of these substances from fixed tissues into the blood stream, one of whose functions is to transport the substances for disposal.

It seemed of interest to investigate this aspect of the problem. For that purpose animals were nephrectomized and the N.P.N. of the blood and spinal fluid was followed as the animal developed uraemia. When the N.P.N. had reached a high level in these two fluids the animal was sacrificed and blocks of tissue were immediately frozen, ground up, and N.P.N. estimations done on these by Dr. Gornall. Chart 2 indicates the state of affairs here. When

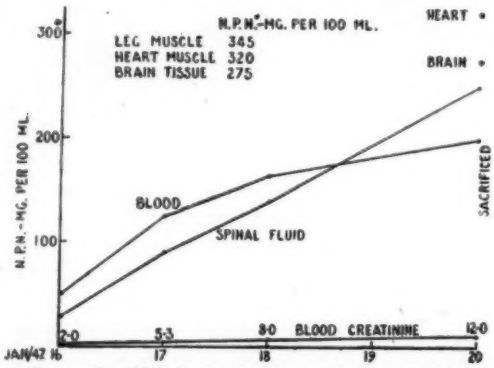


CHART 2.—N.P.N. levels in a male dog weighing 12 kg. after left nephrectomy and ligation of right ureter.

the blood N.P.N. reaches a certain level the spinal fluid level is above this, and the level of the N.P.N. substances in the tissue examined was above that level again. This would tend to bear out the point already made that the blood is only a medium for the collection of these substances and washing away of them for disposal.

When, therefore, in a clinical patient it was reported that 12.97 g. of N.P.N. substances was removed and readings of the blood showed only a slight depression of the N.P.N. level it was obvious that the N.P.N. substance removed was bringing down the level of these toxic substances in the vital fixed tissues of the patient, and the proof of this was the clinical improvement, with diminishing signs of toxaemia, even though the blood N.P.N. was still at a fairly high level.

From the events observed in animals and clinically, we think it can be assumed with fair certainty that, while N.P.N. substances can be removed, there are other substances that are also removed by this dialysing system. These substances are probably responsible in large part for the severe toxaemia and ultimately for death. Proof of this is the fact that in a normal animal from four to ten times the amount of urea necessary to place the N.P.N. at a high level can be given without much injurious effect. Probably, therefore, another substance is responsible for the toxaemia. This substance has not yet been separated and has not been described or analysed, but this system offers an excellent method of approach to the study of such substances, as suggested by Abel, Rowntree, and Turner (1913, 1914).

This work represents some early excursions into a field which offers great prospects for expansion. The method might be used therapeutically to remove toxic substances as well as to administer substances which may be beneficial for the individual.

Several tests have been made on patients to assess the functioning of the apparatus. The cases reported illustrate the ability of this apparatus to perform what was intended.

Case 1

The patient, a woman aged 26, had anuria for a period of nine days after an attempt at induced abortion. During these nine days she was passing about 35 ml. of urine daily, and when first seen was in a state of uraemia. She was comatose, was having mild uraemic convulsions, was severely oedematous, and was not passing urine. She was seen by the physicians, the gynaecologists and the genito-urologists, all of whom agreed that her case was utterly hopeless; in fact, they had given up treatment except for some diathermy which was being applied through the loins.

On the ninth day the patient was attached to this artificial kidney by passing a catheter through the saphenous vein into the inferior vena cava on the right side, and another into the femoral vein on the left. With the machine running for one hour she was moderately improved. The results of the run are shown in Chart 3.

Towards the end of the hour the patient showed some discomfort. She developed a fairly severe chill. Because of this and not knowing just what the effects were, and because of difficulty in following the chemistry accurately, the dialysis was discontinued at the end of an hour. It was shown fairly conclusively on subsequent runs without any similar ill effects that the probable trouble was inadequate washing of the tubing. On all occasions we used new tubing throughout, including rubber tubing, the tambour in the pump, and the dialysing membrane. On the subsequent occasions this was thoroughly washed through with distilled water for an adequate period of time and then washed for a short time with blood solution to remove any remaining substances either in the dialysing membrane or in the tubing. On subsequent runs lasting up to eight hours there were no ill effects whatever in the form of thermal reactions, changes in respiration, pulse rate, blood pressure, or otherwise.

Following the treatment the patient was considerably improved clinically. The next day her condition was fair.

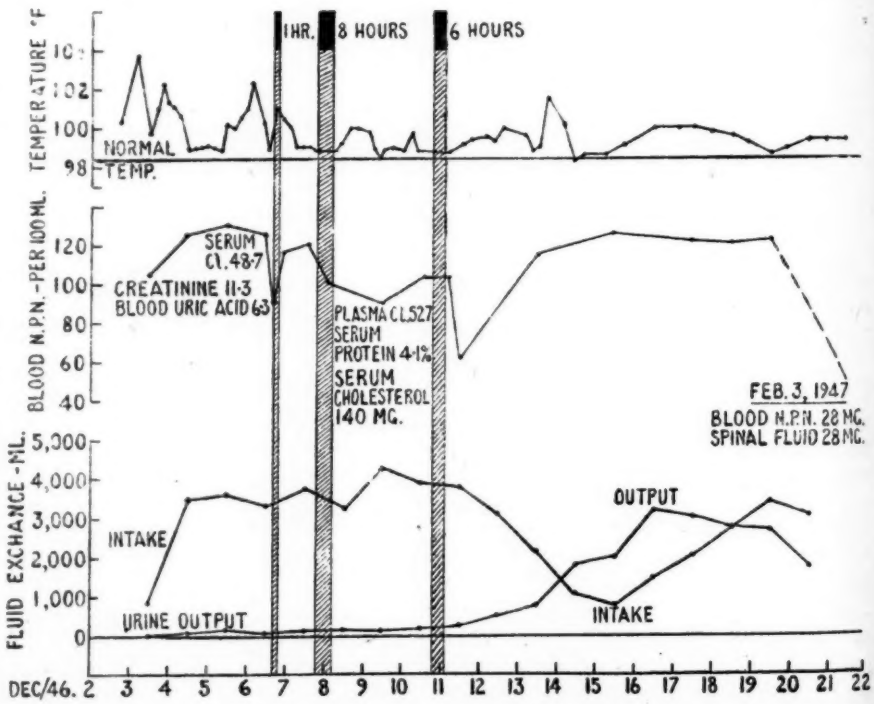


CHART 3.—Case 1. The shaded columns on the sixth, eighth, and eleventh days show the period of dialysis with the artificial kidney. The fall to normal of the blood N.P.N. on February 3 is indicated.

The day after that she was much worse again and another run of eight hours was given on the machine. The results of this are shown in Chart 3. Her condition was very greatly improved. There was still only 45 ml. of urine. Three days later the patient's condition was again serious and another run of six hours was given. The clinical improvement of the patient was very striking. She was comatose at the beginning of each one of these runs on the machine; at the end she was quite bright. The delirium and coma had disappeared. The patient would drink small quantities of fluid, would respond to questions and conversation, and stated that she felt much better. In spite of the pronounced oedema there was some appearance of intelligence in her face.

During the runs on the machine samples of blood, ascitic fluid from the peritoneal cavity, and spinal fluid were removed, and N.P.N. and other tests done on these.

After the last dialysis there was a moderate secretion of urine, and next day there was an enormous secretion of 4,000 ml. of urine. Subsequently the patient made a progressive and uninterrupted recovery and returned to normal health. During the next two weeks samples of both blood and spinal fluid showed a progressive fall of N.P.N., until on the twenty-fifth day these had both reached normal. The oedema had entirely disappeared. The patient was up and about, and was in normal health. At this stage the gynaecologists reported that the foetus was not present in the uterus. While there was no record of its escape, I think one cannot assume that the dialysing apparatus removed it by this means. The patient was in hospital 33 days.

The only remaining abnormality was a lack of concentration on the two-hour test. The urinalysis otherwise was quite normal and the two-hour test showed a concentration only up to 1012. However, as shown on the final point on Chart 4,

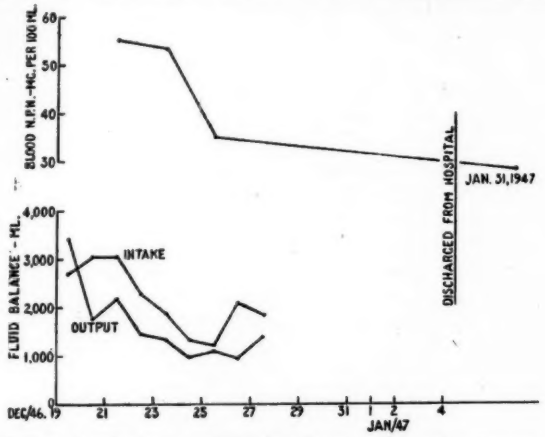


CHART 4.—Case 1. Showing later stages of recovery. N.P.N. and water balance returned to normal.

on the sixty-first day the blood N.P.N. was 28 mg. per 100 ml. The spinal fluid N.P.N. was also 28 mg. per 100 ml., and the two-hour test showed considerable improvement. Here the concentration went up to 1018, and the day and night quantities were fairly normal. The patient has gone back to her regular work and is in normal health. She has since married and given birth to a normal child. Kidney function was watched closely throughout pregnancy, and at no time was there evidence of toxaemia or impaired function.

Case 2

A married woman aged 40 was seen by the courtesy of Dr. J. Crosbie. After caesarean section, when a blood transfusion was given, there was oliguria, and the urine contained haemoglobin and haematin. She passed only 3 to 5 ml. of urine daily for eight days, at which time the blood N.P.N. was 179 mg. per 100 ml. and the patient was showing signs of uraemia.

She was then treated for 26 hours with the artificial kidney. Fifty-four feet (16.5 metres) of tubing was used and 70 g. of N.P.N. was removed from the blood. The following day the urinary secretion increased to 210 ml., rising to 6,730 ml. on the fifth day. The patient gradually improved, and has made an excellent recovery. Renal function has returned to normal and she is in normal health.

There has been survival in about 50% of the patients treated. Those who succumbed were found on the whole to have had chronic kidney disease, and even though the purification of the blood was accomplished satisfactorily they relapsed into a uraemic state.

We wish to thank Professor Van Wyke and Professor J. McClelland for providing some of the patients. We acknowledge with thanks the privilege of laboratory space and the use of some chemicals provided by Professor Andrew Hunter. The assistance of Dr. Allan G. Gornall in doing N.P.N. assays of tissues is acknowledged with thanks. Otherwise the work was carried on independently of the University or other assistance.

REFERENCES

Abel, J. J., Rowntree, L. G., and Turner, B. B. (1913). *Trans. Ass. Amer. Phys.*, **28**, 51.
—— —— —— (1914). *J. Pharmacol.*, **5**, 275, 611.
Kolf, W. J., and Van Noordwijk, J. (1946). *The Artificial Kidney*. J. H. Kok, Kampen, Holland.
McBain, J. W., and Kistler, S. S. (1928). *J. gen. Physiol.*, **12**, 187.
—— —— (1929). *J. phys. Chem.*, **33**, 1806.
—— —— (1930). *Trans. Faraday Soc.*, **26**, 157.
—— —— (1931). *J. phys. Chem.*, **35**, 130.
Murray, G., Delorme, E., and Thomas, N. (1947). *Arch. Surg., Chicago*, **55**, 505.
Seligman, A. M., Fine, J., and Frank, H. A. (1946). *Ann. Surg.*, **124**, 857.
Thalhimer, W. (1938). *Proc. Soc. exp. Biol., N.Y.*, **37**, 641.
Trueta, J. (1947). *Studies of Renal Circulation*. Blackwell, Oxford.

MALARIA

WITH SPECIAL REFERENCE TO CERTAIN EXPERIMENTAL, CLINICAL, AND CHEMOTHERAPEUTIC INVESTIGATIONS*

BY

N. HAMILTON FAIRLEY, C.B.E., M.D., D.Sc. F.R.C.P., F.R.S.

Wellcome Professor of Tropical Medicine, London School of Hygiene and Tropical Medicine; Physician, Hospital for Tropical Diseases, University College Hospital, London

LECTURE II: CHEMOTHERAPY

The factors which may modify the results obtained by treatment with antimalarial drugs include not only the species of the malaria parasite but the variety or strain of the particular plasmodium implicated. The presence or absence of immunity or partial immunity in the patient is very important, and racial considerations may be relevant. Those of negroid stock are sometimes relatively refractory to infection, while Caucasians show maximum susceptibility.

Regarding strains of parasite, James (1931) reported that the Rome strain required eight times as much quinine as the Indian strain of *P. falciparum* to elicit a satisfactory therapeutic response; both strains were equally susceptible to "atebrin" (mepacrine). The Madagascar strain of *P. vivax* was twice as susceptible to "neosalvarsan" (neoarsphenamine) as the local Dutch strain.

Variations in the sensitivity of different strains of the same species of parasite to a given antimalarial drug illustrate the inadvisability of assuming that because a drug in a certain dosage is effective in one geographical area it will necessarily be equally so in another. This point will be specifically illustrated later with reference to mepacrine and proguanil in New Guinea strains of *P. falciparum*.

*Second of the Croonian Lectures delivered at the Royal College of Physicians of London on May 3 and 5, 1949.

The antimalarial drug or combination of drugs used may vary according to the stage, or stages, of the life cycle of the parasite on which the chemotherapeutic attack is made —i.e., the pre-erythrocytic cycle, the asexual blood parasites, the late exo-erythrocytic forms, or the gametocytes.

Prevention and Suppression of Malaria by Chemotherapy

Precise knowledge regarding the suppressive and prophylactic value of antimalarial drugs in non-immunes was very unsatisfactory at the outbreak of hostilities in 1939. The entry of Japan into the war in November, 1941, found the Allies unprepared for warfare in tropical climates and especially for using their non-immune troops in hyperendemic areas of malaria. Malaria casualties in the South-West Pacific and South-East Asia in 1942 were very grave. Some 90% of the forces operating in the Solomons and New Guinea developed severe malaria within four months, and in all these campaigns the type of malaria breakdown was constant. Malignant tertian malaria was responsible for approximately 80–90% of overt attacks during actual jungle fighting, the remaining 10–20% being caused by benign tertian malaria. Later, after a full course of quinine–mepacrine–pamaquin therapy, troops relapsed predominantly with benign tertian malaria, recrudescences of falciparum malaria being uncommon provided reinfection had not taken place.

The malaria problem was one of great gravity, and Allied military and medical authorities decided that every possible channel should be explored to increase the effectiveness of the control of malaria in the forward areas, and that special efforts should be made to discover more potent antimalarial drugs for its control and prevention in jungle warfare. In this connexion a large medical research unit was established at Cairns, in Northern Australia, for the specific purpose of investigating the effectiveness of various antimalarial drugs in experimentally infected Australian Army volunteers living in the Tropics and tested under conditions simulating jungle warfare. During these researches some 850 healthy volunteers were experimentally infected with sporozoite-induced malaria, using strains of *P. falciparum* and *P. vivax* from New Guinea and New Britain. Despite intense hyperinfection none of these volunteers died from malaria, and though subinoculation was practised on a scale never previously attempted no ill effects were noted. The subinoculation technique adopted by Fairley (1945) and Fairley *et al.* (1946a, 1947) afforded data which enabled antimalarial drugs to be classified into one of two groups:

1. *Schizonticidal suppressants*—i.e., those which exerted suppressive and possibly curative effects by schizonticidal action after asexual parasites had appeared in the blood. The drugs which were found to produce suppression of malaria by schizonticidal action on the asexual erythrocytic parasites included quinine, sulphadiazine and allied drugs, mepacrine, "sontochin," and "chloroquine." While taking an effective suppressant dose of these drugs each day, subinoculation of 200 ml. of blood collected on the seventh day after exposure of the donor to infection with *P. falciparum* and on the ninth day with *P. vivax* invariably led to malaria in the recipient, showing that suppression was achieved by schizonticidal action and not by its effects on pre-erythrocytic forms of the parasite.

2. *Causal prophylactics*—i.e., those which acted on sporozoites or pre-erythrocytic forms, either destroying them before they gave rise to asexual erythrocytic parasites (complete causal prophylaxis) or temporarily inhibiting or modifying their schizogonous cycle so that the appearance of asexual erythrocytic parasites in the circulating blood was delayed and the incubation period prolonged (partial causal prophylaxis). Subinoculations made on the seventh day in *P. falciparum* infections and on the ninth day in *P. vivax* infections were invariably negative. Only the biguanides or the 8-amino-quinolines fall into this category. As all the more important antimalarial drugs were tested at Cairns for suppressive and prophylactic purposes under experimental conditions not available elsewhere, my remarks on the control of malaria by chemotherapy will largely be based on these researches.

1. Schizonticidal Suppressants

Quinine

Quinine sulphate in a dosage of 10 gr. (0.65 g.) daily proved ineffective as a suppressant against malaria resulting from mosquito-transmitted New Guinea strains of *P. vivax* and *P. falciparum*. When the daily dose was increased to 20–30 gr. (1.3–2 g.) suppression was complete; radical cure resulted in falciparum malaria provided this dosage was continued for 23 days after exposure, though not in vivax malaria. With this high dosage parasites were not demonstrated in thick smears, but subinoculations were positive on the seventh day in malignant tertian infections, showing that radical cure was obtained by schizonticidal action, not by a causal prophylactic effect.

As 10 gr. of quinine approximated to the maximum daily dose that could generally be tolerated for any prolonged period, it was evident that quinine was unsuitable for suppressive purposes in the South-West Pacific. With certain Indian and African strains of *P. falciparum* and *P. vivax* a daily dose of even 5 gr. (0.32 g.) of quinine effectively suppresses malaria, but after medication ceases overt malignant tertian and benign tertian malaria develop.

The great drawback to quinine as a suppressive drug is that it so often fails to produce radical cure of malignant tertian malaria in the usual suppressive dosage and leads to a condition of chronic latent or chronic recrudescing malignant tertian malaria, in the presence of which true blackwater fever is apt to develop. For this reason, if for no other, quinine is unsuitable for suppressive purposes in Europeans. Blackwater fever practically disappeared from New Guinea and elsewhere in the South-West Pacific with the radical cure of malignant tertian malaria in the early stages of the infection. This was occasioned by the introduction of mepacrine for suppressive purposes and for the treatment of the clinical attack. A similar result was recorded by Findlay and Stevenson (1944) in West Africa.

Sulphonamides

Coatney and Cooper (1948) record that prophylactic action against gallinaceum malaria in birds has been demonstrated for over 30 sulphonamide derivatives since they established early in 1942 that sulphadiazine would prevent this infection (Coatney and Cooper, 1944). Several years earlier "proseptasine" in large dosage had been reported to have true prophylactic action against *P. falciparum* by Sinton, Hutton, and Shute (1939), and late in 1942 high hopes existed in the U.S.A. that sulphamerazine would prove a true causal prophylactic for human species of malaria parasites. In 1943 supplies of sulphamerazine were sent from the U.S.A., and that drug, along with sulphadiazine and sulphamezathine, was fully investigated by Fairley (1945) for prophylactic action in human malaria, unfortunately with disappointing results.

In vivax malaria all these drugs proved ineffective suppressants of both trophozoite and sporozoite experimentally induced infections, even in a dosage of 1 g. daily. In falciparum malaria they proved good suppressants and generally brought about radical cure. Though parasites were rarely demonstrable in thick blood smears, subinoculations on the seventh day after exposure to infection were

positive—a result which showed they were not true causal prophylactics in man. Owing to their failure to suppress vivax infections and because of toxic effects such as agranulocytosis, it was decided that these sulphonamides should not be used in the South-West Pacific for malaria suppression.

Using sulphadiazine and sulphapyrazine, Coatney *et al.* (1947a, 1947b) reported similar experimental findings in volunteers infected with the McLendon strain of *P. falciparum* and the St. Elizabeth strain of *P. vivax*.

Mepacrine ("Atebrin")

Though the dosage of mepacrine advised in the South-West Pacific had been one tablet daily (0.1 g.), malaria casualties in the Huon Peninsula campaign in 1943 were devastating. The ratio of medical : battle casualties was 15 : 1; malaria constituted over 60% of the medical casualties. There was definite evidence that mepacrine discipline was poor and that the drug was not being regularly taken.

Later in the same year excellent results were obtained in volunteers at Cairns receiving one tablet (0.1 g.) of mepacrine on six or seven days of the week for four weeks before exposure to infection, during the period of exposure, and for 23 days after the last infective bite (New Guinea strains). Controls not taking the drug, who were bitten by the same number of infective mosquitoes from the same batch, invariably developed malaria.

1. *Benign Tertian Malaria.*—Though volunteers infected with *P. vivax* did not develop attacks of overt malaria when receiving mepacrine in the above dosage, overt malaria developed two to seven weeks after stopping the drug.

2. *Malignant Tertian Malaria.*—Volunteers repeatedly exposed to 10 to 20 infective bites (*P. falciparum*) failed to develop overt malaria when following an identical suppressive mepacrine regimen. Mild clinical features associated with slight transient rises in temperature, fleeting aches and pains, and perhaps some tenderness or temporary enlargement of the liver and spleen were sometimes noted, but symptoms were never severe enough to necessitate rest in bed, and the volunteers invariably carried on their routine activities. Despite these minor symptoms parasites were rarely, if ever, demonstrable in thick blood films during exposure to infection while taking mepacrine, though subinoculations might be positive. After cessation of the drug overt malaria failed to develop, subinoculations were negative, and on superinfection volunteers showed normal susceptibility—i.e., they developed overt malaria when they were reinoculated with blood containing the same strain of *P. falciparum*. These findings constituted a chain of evidence indicating that malaria infection had been either prevented or cured. Early subinoculation from the seventh to the 11th day after infection or reinfection, however, had revealed parasites in the blood even though they could not be demonstrated microscopically. It was therefore evident that in malignant tertian malaria mepacrine was not acting as a causal prophylactic, but was producing radical cure by schizonticidal action, destroying the young asexual parasites after they had gained access to the circulation.

3. *Mixed Infections with P. falciparum and P. vivax.*—In jungle warfare troops were generally infected with both *P. falciparum* and *P. vivax*. To reproduce field conditions experimentally it was necessary to infect volunteers repeatedly over a period of several months by exposure to vivax- and falciparum-infected mosquitoes. In addition it was essential to subject these volunteers to conditions generally believed to favour malaria relapses, such as physical fatigue, cold, anoxia, blood loss, etc.; all this was done, but in no instance did overt malaria develop while they were taking mepacrine. On an average of 30 days after cessation of mepacrine, volunteers developed overt benign tertian malaria; falciparum parasites, however, were not found.

These experiments were of considerable significance from a military point of view. They indicated that where similar strains of *P. falciparum* abounded troops could fight in hyperendemic areas of malaria without significant malaria casualties provided they were taking mepacrine in adequate daily dosage: in addition they implied that there should be no deaths, no malaria carriers, and no blackwater fever if the daily dose was continued for three to four weeks after leaving the endemic area. After stopping mepacrine, however, troops infected with suppressed vivax malaria would develop overt attacks.

Following receipt of the results of these experiments, military disciplinary measures in regard to mepacrine administration were widely enforced. Malaria casualties rapidly diminished and the experimental findings were confirmed in jungle warfare throughout the South-West Pacific except in 1945 in the limited Itape-Wewak area, on the northern coastline of New Guinea, where moderately severe malaria casualties occurred. Fairley *et al.* (1946b) found that in addition to the universal mepacrine-sensitive strain a relatively insensitive strain of *P. falciparum* was present in troops there which required 0.2 g. daily for its certain suppression and larger doses than usual for therapeutic purposes.

In volunteers infected with the ordinary New Guinea strains the mean plasma mepacrine level of over 20 μg. per litre was found adequate to suppress either vivax or falciparum infections. With the atypical Itape-Wewak strain which was relatively insensitive to mepacrine breakthroughs occurred in volunteers when the plasma mepacrine level was well above 30 μg. per litre. This strain showed no decreased susceptibility to chloroquine or proguanil, and if either of these drugs had been available it could have been substituted in the usual dosage for mepacrine with certainty of success. Bang *et al.* (1946a), as a result of studies on the efficiency of mepacrine suppression in the South-West Pacific, concluded that it was mainly a problem of drug administration and that clinical malaria developed in the presence of inadequate amounts of mepacrine. The concentration of mepacrine present in break-throughs was the same in chronic relapses and primary attacks of malaria. They considered there was no need for a dosage greater than 0.1 g. per day. They also found that in at least 98% of the American troops in strenuous combat who received 1 g. of mepacrine per week (generally in bi-weekly doses of 0.5 g. each) malaria was fully suppressed (Bang *et al.*, 1946b).

The 4-amino-quinolines

Sontochin and chloroquine ("resochin") belong to the 4-amino-quinoline group of compounds which were synthesized by German chemists in 1934 and patented in 1939. They had not then been subjected to extensive biological testing and their clinical study was being attempted by the French at the time of the invasion of North Africa, when sontochin fell into Allied hands. These drugs and others of the group were resynthesized in U.S.A. and tested biologically on a large scale in both bird malaria and man in 1943–4, when they were sent to the Cairns unit to be investigated as suppressants and causal prophylactics. Detailed results, which were summarized by Fairley (1946), were communicated to the National Medical Research Council, U.S.A., in 1944.

The suppressive dosage used was 50–100 mg. daily for chloroquine and 100–200 mg. for sontochin. The results obtained with *P. vivax* and *P. falciparum*, as well as with mixed infections in the field type of experiment, were identical with those obtained with mepacrine. Both drugs

suppressed vivax malaria and suppressed and radically cured falciparum infections. Subinoculations on the eighth day in falciparum infections and on the ninth and tenth day in vivax infection proved positive, showing that infection had occurred and that no inhibitory or lethal action was being exerted on the pre-erythrocytic forms. Subinoculations on the twenty-first day after exposure were negative in falciparum infections, indicating radical cure; none of these volunteers subsequently developed overt malaria. Significant toxic reactions or skin discoloration were not noted with either drug.

Field trials are still in progress, using chloroquine diphosphate in a dosage of 0.5 g. (0.3 g. base) once weekly. Coatney (1949) states that, in Panama, Clarke found that this regimen resulted in almost complete protection against the three common species of human malaria parasite, and Field (1949) has reported very favourable results from Malaya.

2. Causal Prophylaxis by Drug Action on Pre-erythrocytic Forms

Two groups of compounds possess such an action—the 8-amino-quinolines and the biguanides. As it is necessary to use pamaquin or pentaquine in toxic dosage to get a causal prophylactic effect they need not be further considered.

The brilliant researches of Curd, Davey, and Rose (1945) culminated in the synthesis of the biguanides and the discovery of their causal prophylactic and therapeutic action in bird malaria. It was arranged through Dr. C. M. Scott and the Medical Research Council for investigations on their suppressive and causal prophylactic action to be undertaken at Cairns by Fairley and his colleagues (1946a). Over 200 volunteers were used in these experiments on paludrine (proguanil) alone.

Proguanil

When volunteers were exposed to infective biting by falciparum-infected mosquitoes while taking proguanil in a daily dosage of 100 mg. no minor symptoms of malaria appeared, parasites were never demonstrable in the blood by microscopical examination, and subinoculation from the seventh day onwards was invariably negative. This result indicated that the primary wave of erythrocytic merozoites arising from rupture of the pre-erythrocytic schizonts was either delayed or failed to appear. Proguanil administration ceased some 21 days after exposure, and the subsequent failure to develop overt attacks of malaria or demonstrable parasites in the blood indicated that destruction of the pre-erythrocytic parasites had been achieved. In other words the drug was acting as a true causal prophylactic.

Similar results regarding suppression and negative subinoculations were obtained in volunteers experimentally infected with *P. vivax* while taking 100 mg. of proguanil daily, except that after ceasing to take the drug they ultimately developed overt vivax malaria. Proguanil was here acting only as a partial causal prophylactic, inhibiting pre-erythrocytic schizogony but not destroying the tissue phase of the parasite.

Similarly, in field experiments where volunteers were bitten by as many as 250 mosquitoes containing either falciparum or vivax sporozoites in their salivary glands, suppression was complete during the daily administration of proguanil (100 mg.). Some 24 to 33 days after the last dose of proguanil overt vivax malaria developed.

Single-dose Regimen in Prophylaxis

Subsequent experiments showed that proguanil in a single dose of 50–100 mg., given at any time between the 39th and 131st hours after a single exposure to falciparum-infected mosquitoes, acted as a complete causal prophylactic and entirely eradicated infection in the pre-erythrocytic stage. A single dose of 300 mg. given three hours before or three hours after exposure to infection failed to protect; so it did at 168 hours, though at 144 hours it gave protection. These findings indicated that the pre-erythrocytic forms were much more susceptible to the action of proguanil than either the sporozoites or the first generation of erythrocytic merozoites which would be escaping into the circulation about this time—i.e., on the seventh day.

In native labour groups comprising partial-immunes it is convenient to administer a prophylactic drug at weekly intervals. In doing so with proguanil, however, it is important to appreciate that 300 mg. once weekly may not prevent merozoites of even the most proguanil-sensitive strains of *P. falciparum* gaining access to the blood stream if the individual has been infected six to seven days previously. Furthermore the individual would still be vulnerable to reinfection with *P. falciparum* on the eighth day if bitten by infective mosquitoes some hours before or a few hours after the weekly dose of proguanil had been taken. Subsequent suppression and radical cure would then depend on the schizonticidal action of the drug, and if the strain of *P. falciparum* happened to be relatively insensitive to proguanil in this respect occasional break-throughs with overt attacks would not be surprising. In such circumstances, once overt falciparum malaria develops it is essential to establish radical cure before the patient reverts to prophylactic proguanil.

Covell *et al.* (1949b) investigated the causal prophylactic action of proguanil in patients infected with a West African strain of *P. falciparum* which was relatively insensitive to the schizonticidal action of that drug. They found, even with this strain, that complete protection was afforded and malaria prevented by proguanil when given in doses of (1) 50 or 100 mg. daily, (2) 100 mg. twice a week at intervals of three or four days, or (3) 300 mg. once weekly.

With Europeans or non-immunes generally, experience has shown the best regimen to adopt is one tablet (0.1 g.) of proguanil taken regularly every day at the same time so that it becomes a habit. Provided the individual is completely free from malaria when suppressive proguanil is begun, this regimen should lead to the prevention of falciparum malaria and to the suppression of benign tertian and quartan malaria, though not to their radical cure.

Proguanil-resistant Strains

Following the administration of subcurative dosage of proguanil during a series of overt attacks, proguanil-resistant strains have been recorded as developing in *P. gallinaceum* in chicks by Bishop and Birkett (1947) and Williamson, Bertram, and Lourie (1947), and in *P. cynomolgi* in monkeys by Hawking and Perry (1948) and Schmidt *et al.* (1949). Such proguanil-resistance may appear within two and a half months, when the full impact of treatment must fall on the early erythrocytic parasites. Proguanil-resistance, once developed, is retained on successive transmission through both sporozoite-infected birds and monkeys. Rollo, Williamson, and Lourie (1948) failed to produce resistance when the treatment was administered in latent infections—i.e., after the phase of acute parasitaemia—even when treatment twice daily was continued for one

year; in these circumstances treatment fell mainly, if not exclusively, on the exo-erythrocytic forms.

Seaton and Lourie (1949) produced resistance to proguanil in a strain of *P. vivax* by giving small doses of the drug to consecutive patients in whom the strain was being maintained by blood inoculation. The resistance was unaffected by passage through mosquitoes. Resistance was produced under highly artificial conditions over a period of 20 months, but only during the last few weeks had the resistance risen to doses within the range of those ordinarily in use for either suppression or treatment of malaria. They concluded that the danger of producing a serious degree of resistance in a strain of *P. vivax* by the ordinary use of proguanil in clinical practice was slight, if not negligible, both in the treatment of the clinical attacks and in prolonged use of the drug for prophylactic purposes.

In Australia, where many thousands of patients with relapsing vivax malaria were treated with proguanil or other drugs during the acute attack and subsequently received proguanil (0.1 g.) bi-weekly for six months or longer, increased resistance to the drug was not found.

Though proguanil-resistant strains have been produced in man and monkeys experimentally, the conditions underlying their production have been highly artificial. Time alone will reveal if they have practical significance in clinical practice. Fortunately, when a strain of parasite becomes drug-resistant it does so for one particular antimalarial drug or group of drugs and not for others. This appears to be the case whether the resistant strain has been produced experimentally or naturally, as in the Itape-Wewak strain of *P. falciparum* which was relatively insensitive to mepacrine. It follows that when a drug is being used for suppressive or prophylactic purposes the development of specific drug resistance by a given strain of parasite can be circumvented by the substitution of another antimalarial drug of a different group.

Schizonticidal Drugs (Asexual Erythrocytic Parasites)

The clinical cure of overt malaria generally presents little difficulty, while the clinical and radical cure of falciparum malaria in particular is most satisfactory unless there is profound hyperinfection or the strain of parasite is unduly insensitive to the schizonticide employed.

Routine treatment for the overt attack of malaria in the Australian Army consisted of 30 gr. (2 g.) of quinine for three days, mepacrine for the next five days, and pamaquine (base) 10 mg. thrice daily for three to five days. At first mepacrine was given in a dosage of 0.3 g. daily from the fourth to the eighth day; later it was increased to 0.6 g. daily on the fourth and fifth days, and 0.3 g. daily on the sixth, seventh, and eighth days. Then a maintenance dose of mepacrine (0.1 g.) was given daily for six weeks. In all clinically severe cases of overt malaria and in hyperinfections intravenous quinine (10 gr.) was given without delay and repeated where necessary.

This combined therapy was most effective. Radical cure of falciparum malaria generally resulted, carriers were eliminated, and the malaria mortality rate was extraordinarily low, not exceeding 1 per 1,000 in treated cases, including complications.

Quinine.—It has been appreciated for many years that clinical and radical cure of overt malaria by quinine could be achieved with most strains of *P. falciparum* if 10 gr. was administered thrice daily for three weeks. Furthermore, the use of quinine is entirely free from the danger of precipitating true blackwater fever in primary falciparum malaria, as this complication arises only in the presence of chronic latent or recrudescing falciparum infections.

Mepacrine.—The schizonticidal properties of mepacrine were well known before the war, but the work of Shannon *et al.* (1944) in establishing the pharmacological basis for its more rational use was outstanding. Their investigations showed that mepacrine is extensively localized in the tissues and that its effectiveness as a schizonticide is a function of its concentration in the plasma. A large loading dose was recommended during the first day (1 g. in divided doses) to obtain rapid saturation of the tissues and a high plasma level; this resulted in a more rapid clinical response, especially in falciparum malaria.

Reference has already been made to the schizonticidal action possessed by the 4-amino-quinolines when given in suppressive dosage, and this is also manifest in their effectiveness in rapidly controlling clinical attacks.

Chloroquine.—This drug is probably the most potent schizonticide yet discovered. Berliner *et al.* (1947) state that it is superior to mepacrine owing to its lower toxicity, its small dosage, and the small drug concentration required to produce a given effect. Coatney (1949) reports that in falciparum malaria three or four days' treatment with chloroquine gives better results than a week's treatment with mepacrine, and that it is the drug of choice in the treatment of the acute attack. The course advocated consists of 2.5 g. of chloroquine diphosphate administered over three days. Since chloroquine, like mepacrine, is extensively stored in the tissues, a large initial dose (1.5 g.) is advised on the first day of therapy in order to get an adequate plasma concentration. If chloroquine can produce radical cure of the different strains of falciparum malaria with regularity in non-immunes after three days' treatment unassociated with toxic symptoms it is superior to other schizonticides. It produces clinical cure of benign tertian and quartan malaria, but there is no evidence that it is more effective than other schizonticides in producing radical cure.

Proguanil.—Maegraith and his colleagues (1945) treated 22 patients naturally infected with West African strains of *P. falciparum* with proguanil, the dosage varying from 50 to 600 mg. twice daily. The clinical and parasitological response was satisfactory in all instances, but it was not feasible to determine the radical cure rate. Fairley *et al.* (1946a) reported radical cure in 45 out of 46 experimentally induced sporozoite infections and in 41 out of 41 natural infections with New Guinea strains of *P. falciparum*.

Therapeutic trials have been generally satisfactory in Malaya and India, but results in Africa have been widely divergent, some being satisfactory, others the reverse. With the object of clarifying this problem, Covell and his colleagues (1949a) recently investigated the action of proguanil in infections with a West African (Lagos) strain of *P. falciparum* in the treatment of overt attacks. Nine out of 10 patients with overt primary malaria treated with 0.3 g. of proguanil twice daily for 10 days had recrudescences after three weeks. Despite a second similar course, three patients had recrudescences later. When patients infected with this strain received 0.6 g. of proguanil daily for 10 days, reinforced on the first day of treatment by either quinine (2 g.) or mepacrine (0.9 g.), radical cure resulted in all instances. Until more is known about the therapeutic response to infection with falciparum strains in other parts of Africa, and indeed in falciparum infections generally, it would seem advisable to reinforce the schizonticidal action of proguanil with mepacrine. As an alternative to 0.9 g. of mepacrine on the first day only, a dosage of 0.2 g. thrice daily on the first day and 0.1 g. thrice daily on the second and third days should be well tolerated and prove satisfactory for this purpose.

In volunteers infected with New Guinea strains of *P. falciparum* treatment was instituted at variable periods after exposure to infections, from the time sporozoites first entered the blood on the seventh day before fever had started to some weeks after its onset. No significant difference was noted between early- and late-treated cases, so the development of partial immunity could not be the factor responsible for the high radical cure rate obtained.

The most likely explanation of the different therapeutic results is that these two different geographical strains vary

markedly in their sensitivity to the schizonticidal action of proguanil, the New Guinea strain being very sensitive and the Lagos strain relatively insensitive.

Single-dose Regime for Treatment of Overt Malaria

One of the remarkable features of proguanil is that a small single dose of the drug will frequently control the clinical attack. This was first noted at Cairns in several non-immune volunteers who were suffering from overt falciparum malaria with high parasite densities; a single tablet (100 mg.) resulted in clinical cure and temporary disappearance of parasites in thick blood films. Parasites, however, shortly reappeared and clinical recrudescences occurred. A similar effect was also observed in vivax infections.

The advantages of such single-dose therapy among native populations with partial immunity are obvious. Field trials have been made in Malaya, India, and elsewhere—generally with favourable results. The dose usually adopted for this purpose has been 0.3 g. In India, Afridi *et al.* (1947) considered that 0.3 g. was the optimum single dose of proguanil, and found it sufficient for the clinical cure of overt falciparum and vivax malaria in a high proportion of cases. Field (1949) compared the effects of 0.6 g. of mepacrine given on one day in divided doses and one single dose of 0.3 g. of proguanil in the treatment of overt malaria in Malaya. The larger dose of mepacrine was used because it was found that 0.3 g. was not effective in falciparum malaria. The disappearance of parasitaemia was quicker in overt falciparum malaria with proguanil than with mepacrine and slower in benign tertian and quartan overt malaria. The disappearance of fever was slower with proguanil than with mepacrine in all forms of malaria, but the sense of well-being in the proguanil-treated cases was stressed.

In prophylaxis the high suppressive action of proguanil was confirmed in falciparum and vivax malaria, and little difference was noted between a dosage of 0.1, 0.2, or 0.3 g. given once a week.

Drugs Acting on Exo-erythrocytic Forms (8-amino-quinolines)

Clinical cure of vivax malaria with any of the well-known schizonticidal drugs like quinine, mepacrine, or chloroquine is highly satisfactory, but radical cure is not. There is no evidence that any of these drugs destroy the late exo-erythrocytic forms which are responsible for relapses. Proguanil, even in small dosage, is an effective though somewhat slower schizonticide for vivax malaria. It slows up or temporarily inhibits schizogony in the pre-erythrocytic phase if administered over the first week after infection, but there is no evidence that it affects later tissue forms so as to produce radical cure. For such a result we have to turn to the 8-amino-quinolines, of which the best-known compounds are pamaquin, pentaquine, and iso-pentaquine.

Pamaquin.—The first demonstration of the radical cure of vivax malaria by one of these drugs was made by Sinton and Bird (1928) in India. They reported that while 70% of patients with chronic malaria treated with quinine relapsed, only 30% of those treated with pamaquin did so; when quinine was administered simultaneously with pamaquin, as in "plasmoquine co.," the relapse rate was reduced to 8.5%. These results were confirmed in India and elsewhere, but owing to the troublesome toxic effects this effective combined treatment for recurrent vivax infections unfortunately lapsed. It was revived in the later stages of the recent war, and radical cure rates approximating to 80% were generally obtained in natural vivax infections treated with 2 g. of quinine and 30 mg. of pamaquin (base) daily for 12 to 14 days. In Australia proguanil (0.3 g. daily) combined with pamaquin (30 mg. daily) was given for 12 to 14 days, with results which were comparable to those obtained in a similar series treated with quinine and pamaquin, except that relapses appeared somewhat later in the proguanil–pamaquin series. With proguanil (0.3 daily), toxic complications were no more common than with quinine. Monk (1948) concluded that this treatment was likely to prove at least as successful as quinine–pamaquin therapy.

Pentaquine and Iso-pentaquine.—After 1944 much of the American war effort in regard to antimalarials was expended in attempting to find an 8-amino-quinoline derivative which was curative for vivax malaria and less toxic than pamaquin. Alving *et al.* (1947) in a clinical trial of 18 analogues of pentaquine concluded that per kilogram of body weight pentaquine has greater curative activity and lower toxicity than pamaquin. Coatney (1949) reports two of these compounds—pentaquine and iso-pentaquine—to be superior to pamaquin. The dosage generally advocated consists of quinine sulphate 2 g. and pentaquine (base) 60 mg. daily for 10 to 14 days. Its radical curative action in overt vivax malaria has been shown by Loeb (1946), Monk (1948), and others. White *et al.* (1948) have also shown that this treatment is just as effective when given during the latent phase of *P. vivax* in the complete absence of erythrocytic parasites. The action of the drug in these circumstances can only be on late exo-erythrocytic forms.

Identical toxic reactions appear to arise with pamaquin, pentaquine, and other 8-amino-quinolines. They include gastro-intestinal disturbances, methaemoglobinanaemia, and haemolytic anaemia supervening on the third to fifth day of treatment. Rosenfeld, Zubrod, *et al.* (1948) and Blake (1948) found that methaemalbumin consistently appeared in the serum of individuals receiving quinine and pamaquin concurrently. These findings signify that the administration of quinine and pamaquin and probably other 8-amino-quinoline derivatives is always associated with some degree of intravascular haemolysis, which in certain instances produce frank haemolytic anaemia and in rare cases haemoglobinuria.

The toxic manifestations and the radical-cure rate in vivax malaria, associated with pentaquine–quinine and pamaquin–quinine combined treatments, seem so similar that it is difficult to assess their exact status at the present time. Treatment with any of the 8-amino-quinoline group of drugs should be under medical supervision.

Gametocidal Drugs

The treatment of the malaria carrier has often attracted less attention than it merited. In hyperendemic areas of malaria effective carriers are found essentially in infants and young children and not in the older members of the community who have become immune as a result of repeated infection. The individual possessing solid immunity and tolerance may harbour asexual but not sexual parasites in the blood. On the other hand, non-immune adults who develop primary malaria become effective carriers if the primary trophozoite wave is not rapidly cut short by therapy; this is a major factor in the development of epidemics in unsalted troops in malarious areas.

While quinine and mepacrine are reasonably effective primary gametocides in infections with *P. vivax* and *P. malariae*, they do not exert any deleterious action on the mature gametocytes of *P. falciparum*. Pamaquin, on the other hand, is a polyvalent gametocide and even in minute doses (10–20 mg. base) renders falciparum gametocytes non-infectious to mosquitoes within 24 hours, and causes their disappearance from the blood in three to four days.

Mackerras and Ercole (1947) found that when proguanil was given in a dosage of 0.1 to 0.3 g. daily to falciparum or vivax gametocyte carriers (New Guinea strains) no effect was observed on the number or microscopical appearance of the gametocytes in the blood. Only when given very early in the attack was gametocyte production affected by proguanil, and then only indirectly, because the primary trophozoite wave was checked before gametogony had started.

In the stomach of the mosquito ingested falciparum or vivax gametocytes may undergo exflagellation and fertilization and even produce small oöcysts, but development ceases at this point and the oöcysts die if proguanil is present even in small quantities in the blood feed. Complete sterilization of the gut infection in mosquitoes results some one to two hours after 0.15 g. of proguanil has been administered to a carrier. In mosquitoes fed on the second day vermicules may form, but in those fed on the third or fourth day of proguanil administration neither vermicules nor oöcysts are detected. The same effect was produced by letting mosquitoes first engorge partially on a normal person taking 0.1 g. of proguanil daily and then allowing them to complete their feed on a carrier with plentiful gametocytes in the blood.

Shute and Maryon (1948) confirmed these findings with the Rumanian strain of *P. falciparum* and suggested it was the female gametocytes on which the drug acted.

These experimental findings imply that it would be difficult for salivary-gland infections to become established in the local anophelines when they are feeding on the blood of people who are taking proguanil regularly. Thus the daily administration of proguanil to a military force in a hyperendemic area would not only be acting as a causal or partial causal prophylactic in individuals inoculated with sporozoites but by inhibiting the development of the sexual cycle in the mosquito it would be a potent factor in limiting transmission and preventing the development of epidemics.

Comment and Conclusions

In conclusion, I would remark that during the past decade we have learnt how to use and when not to use the older antimalarial drugs like quinine, pamaquin, and mepacrine. During this period several potent antimalarial drugs have been discovered or rediscovered and their therapeutic action worked out with considerable exactitude. Proguanil is unique among these owing to (1) its true causal prophylactic action in falciparum malaria, (2) the schizonticidal effect often exerted by a single small dose in overt malaria, and (3) its polyvalent gametocidal properties. Chloroquine is probably the most potent schizonticide yet discovered ; it is of great value both as a schizonticidal suppressant given once weekly and in the intensive treatment of the overt attack. For the radical cure of benign tertian malaria pentaquine and iso-pentaquine are now becoming available ; just how superior they are to pamaquin when given in combination with quinine future work will decide.

Malaria casualties in non-immune troops operating in hyperendemic areas could be prevented or kept at an insignificantly low level by the routine administration under supervision of such drugs as mepacrine, proguanil, and chloroquine in correct dosage. During military operations it would be advisable to have stock-piles of two such antimalarial drugs for suppressive or prophylactic purposes, since the development of resistance to any particular antimalarial drug is specific and can be circumvented by the substitution of another drug of a different group.

References

Afridi, M. K., *et al.* (1947). *Indian J. Malariol.*, **1**, 221.
Alving, A. S., *et al.* (1947). *J. clin. Invest.*, **27**, 34.
Bang, F. B., *et al.* (1946a). *Amer. J. trop. Med.*, **26**, 649.
—— *et al.* (1946b). Ibid., **26**, 753.
Berliner, R. B., *et al.* (1947). *J. clin. Invest.*, **27**, 98.
Bishop, A., and Birkett, B. (1947). *Nature*, **159**, 884.
Blake, W. D. (1948). *J. clin. Invest.*, **27**, 144.
Coatney, R. G. (1949). *Bull. Pan-Amer. San. Bureau*, **28**, 27.
—— and Cooper, W. C. (1944). *Publ. Hlth Rep., Wash.*, **59**, 1455.
—— —— (1948). *J. Parasit.*, **34**, 275.
—— *et al.* (1947a). *Amer. J. Hyg.*, **46**, 84.
—— *et al.* (1947b). Ibid., **46**, 105.
Covell, G., Nicol, W. D., Shute, P. G., and Maryon, M. (1949a). *Trans. R. Soc. trop. Med. Hyg.*, **42**, 465.
—— —— —— —— (1949b). Ibid., **42**, 341.
Curd, F. H. S., Davey, D. G., and Rose, F. L. (1945). *Ann. trop. Med. Parasit.*, **39**, 208.
Fairley, N. H. (1945). *Trans. R. Soc. trop. Med. Hyg.*, **38**, 311.
—— (1946). *Schweiz. med. Wschr.*, **76**, 925.
—— *et al.* (1946a). *Trans. R. Soc. trop. Med. Hyg.*, **40**, 105.
—— *et al.* (1946b). Ibid., **40**, 229.
—— *et al.* (1947). Ibid., **40**, 621.
Field, J. W. (1949). Second Interim Report to the Malarial Subcommittee of the Colonial Medical Research Committee, p. 23. (unpublished).
Findlay, G. M., and Stevenson, A. C. (1944). *Ann. trop. Med. Parasit.*, **38**, 168.
Hawking, F., and Perry, W. L. M. (1948). *Lancet*, **2**, 850.
James, S. P. (1931). *Trans. R. Soc. trop. Med. Hyg.*, **24**, 477.
Loeb, R. F. (1946). *J. Amer. med. Ass.*, **132**, 321.
Mackerras, M. J., and Ercole, Q. N. (1947). *Trans. R. Soc. trop. Med. Hyg.*, **41**, 365.
Maegraith, B. G., *et al.* (1945). *Ann. trop. Med. Parasit.*, **39**, 232.
Monk, J. F. (1948). *British Medical Journal*, **1**, 1221.
Rollo, I. M., Williamson, J., and Lourie, E. M. (1948). *Ann. trop. Med. Parasit.*, **42**, 241.
Rosenfeld, M., Zubrod, C. G., *et al.* (1948). *J. clin. Invest.*, **27**, 138.
Schmidt, L. H., Genther, C. S., Fradkin, R., and Squires, W. (1949). *J. Pharmacol.*, **95**, 382.
Seaton, D. R., and Lourie, E. M. (1949). *Lancet*, **1**, 394.
Shannon, J. A., Earle, D. P., Brodie, B. B., *et al.* (1944). *J. Pharmacol.*, **81**, 307.
Shute, P. G., and Maryon, M. (1948). *Parasitology*, **38**, 264.
Sinton, J. A., and Bird, W. (1928). *Indian J. med. Res.*, **16**, 159.
—— Hutton, E. J., and Shute, P. G. (1939). *Ann. trop. Med. Parasit.*, **33**, 47.
White, W. C., *et al.* (1948). *J. nat. Malaria Soc.*, **7**, 316.
Williamson, J., Bertram, D. S., and Lourie, E. M. (1947). *Nature*, **159**, 885.

THE NATURAL HISTORY OF ASTHMA

A REVIEW OF 300 CASES

BY

ELSIE O. WILLIAMS, M.B., Ch.B., D.P.H.

AND

G. E. O. WILLIAMS, M.D., M.R.C.P.

Assistant Physician, Birmingham United Hospital ; late Medical Registrar, Liverpool Royal Infirmary

It is known that asthma is a disease varied in its causation but unvarying in its mechanism, essentially involving contraction of the smooth muscle of the bronchioles. This contraction may occur in response to any of a wide range of stimuli—inflammatory, allergic, mechanical, reflex, psychological, endocrine. Such factors may be "aetiological" (inducing the first of the patient's attacks) or "aggravating" (being concerned in the precipitation of subsequent attacks). The former may act either centrally, by increasing the patient's sensitivity to asthmogenic agents, or peripherally, by producing a permanent state of irritability of the respiratory mucosa or musculature, whereby an attack of asthma occurs in response to appropriate stimulation. Aetiological and aggravating factors may be identical or they may be apparently unrelated. For example, in many instances asthma may be initiated by some endocrine crisis such as puberty or pregnancy, or by acute respiratory infection, but the same patient may nevertheless have subsequent attacks brought on by a

completely different aggravating factor such as dust, exertion, or psychological shock.

In brief, the genesis of asthma may be said to be a triple phenomenon, depending, first, upon the establishment of the "asthma diathesis," in which a family history of allergic diseases, previous allergic manifestations in the patient, and organic abnormalities in the bronchial tree or upper respiratory tract are also known to be significant. The other essential elements are the presence of aetiological factors and exposure to aggravating stimuli.

With a view to correlating the rates of incidence of the above factors and assessing their relative significance the case records of some 300 cases treated at the Liverpool Royal Infirmary Asthma Clinic between 1935 and 1940 have been surveyed.

Signs of the "Asthma Diathesis"

Family History.—Previous allergic disease in the family was found in 51% of 147 males, and in 50.6% of 158 females. In this series at least one member of the patient's family (parents, grandparents, brothers, sisters, uncles, aunts, or cousins) had suffered from asthma, hay-fever, urticaria, eczema, migraine, or epilepsy. Sometimes there were many such instances in the family, and it was found that 22.5% of the males, and 24% of the females had two or more members of the family so affected. Of 141 non-asthmatic patients in the same hospital, a group representing the same class of population, only 12.2% gave "positive" family histories. These findings are very similar to those of Coke (1927) but differ from those quoted by Witts (1934), who found a 60% incidence of "positive" family histories, and more significant than those of Pearson (1934) and Vaughan (1933), who quote much higher rates of incidence of allergy in families of normal subjects.

Age Incidence.—The present series comprised in all 294 patients—141 males and 153 females. They were classified into two main groups—"F.H. positives" with an allergic family history, and "F.H. negatives" with no such family history—and the incidence of asthma beginning at different age groups is shown in Table I.

TABLE I.—*Incidence of Asthma Related to Sex, Ages of Onset, and Family History*

Age Group	Sex		F.H. Positive	
	Male	Female	Male	Female
0–10 years	60	36	63·3%	75·0%
11–20 ,, ...	21	40	57·1%	45·0%
21–30 ,, ...	18	35	28·0%	34·3%
31–40 ,, ...	13	24	53·8%	54·2%
41–50 ,, ...	14	9	35·7%	44·4%
Over 50 ,, ...	15	9	26·7%	33·3%
Total	141	153	50·0%	50·0%

Possible Effect of Menstruation and Pregnancy in Production of Asthma.—Figs. 1 and 2 illustrate the relative ages at *onset* of asthma in the two sexes, and in Fig. 1 the incidence of "positive" family histories in each age group is also shown. There appears to be quite a close parallel between the incidence of positive family histories in the two sexes and at similar ages of onset (see Table I), but the female incidence curves C and D (Fig. 1) and A (Fig. 2) cross the male incidence curves A and B (Fig. 1) and B (Fig. 2) respectively at age groups 11–20 and remain higher until the ages at onset exceed 40 years, after which the figures in each case become similar. This suggests the possibility of some factor or factors having a different effect in the two sexes, beginning approximately at the time of puberty and having in females an aggravating effect upon the asthma. Female endocrine functions seemed significant in this respect, and reference was therefore made to details of female cases in which the onset of asthma occurred between the ages of 14 and 50 years and in which there was a clear history of aggravation by menstruation, pregnancy, or a combination of both. Of 62 cases in which the ages of onset of asthma were stated, the numbers falling into each decade are shown in Table II.

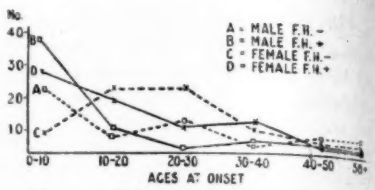


FIG. 1.—Relative incidence of asthma at different ages and subdivided according to sex and family history.

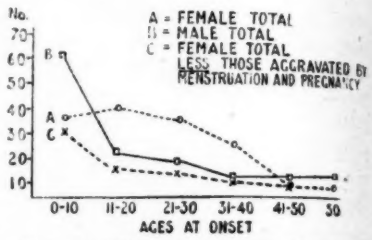


FIG. 2.—Relative incidence of asthma at different age groups, subdivided according to sex and incidence of menstrual or pregnancy aggravation.

TABLE II.—*Incidence of Asthma Aggravated by Menstruation and/or Pregnancy, With Ages of Onset of Symptoms*

Age of Onset:	0–10	11–20	21–30	31–40	41–50
No. of patients ..	5	24	21	11	1

If all such patients are excluded from the total number of females in each age group the remainder represents those in which there is no apparent association with pregnancy or menstruation. They are shown in curve C (Fig. 2), a striking feature of which is its close similarity to that found in males (curve B). Statistical analysis of the figures illustrated by the curves A, B, and C in Fig. 2 shows that the difference between A and B is greater than is likely to be caused by chance ($\chi^2=22.1$, $\eta=5$, $P<0.01$) and that curves C and B differ by amounts which cannot exclude chance as a possible cause ($\chi^2=5.9$, $\eta=5$, $P=0.3$). These findings suggest, therefore, that a proportion of cases of asthma in females may be due to causes associated in some way with female reproductive activity. While it is freely admitted that other associated factors such as psychological changes or reflex sensitivity otherwise enhanced may in many patients have a more direct bearing on the association of asthma with menstruation, evidence is not lacking (Zondek and Bromberg, 1947) that allergic hypersensitivity to the patient's own hormones is by no means rare and may be demonstrated by appropriate skin tests.

Cutaneous Hypersensitivity.—Cutaneous hypersensitivity tests were performed, using Bencard's intradermal and scratch tests for the usual series of allergens. Results were available in 211 cases, and were positive in 35.5%. No comparable series of normal controls was tested, but other workers, such as Pearson (1943), report 20% of positive findings in normal persons, whilst in asthmatic patients the incidence of positives was 75%. On the other hand, Witts's (1934) figures show 40% of positives only among those affected.

It was found that 26 out of 100 "F.H. − " cases were positive to skin tests, while 44% of 111 "F.H. + " cases were positive also on skin-testing. The standard error of these two proportions being 6.42, this difference in the incidence of positive skin tests appears to be statistically significant.

Previous Allergic Manifestations.—Of 246 cases in which the information was available, 40.24% gave a history of one or more of the usually suspected "allergic" manifestations, consisting of the following:

Hay-fever (or vasomotor rhinorrhoea)	39
"Eczema" (including infantile eczema)	54
Migraine	5
Urticaria	12
Epilepsy	2

In 13 cases two of the above conditions occurred together, thus: epilepsy and hay-fever, 1; eczema and hay-fever, 4; migraine and hay-fever, 3; urticaria and eczema, 1; urticaria and migraine, 1; eczema and migraine, 1; urticaria and hay-fever, 2.

It is observed that migraine, though occurring in five patients, does not appear alone, being combined with hay-fever, urticaria, or eczema. Epilepsy occurs once by itself, and once in combination with hay-fever. These findings correspond to those of Witts, in whose series 40–50% of patients had other allergic manifestations, and of Coke, who reports that 22% of his patients had suffered previously from eczema.

Aetiological Factors

Information about factors associated with the onset of asthma was available in 276 cases. The results are shown in Table III. Some light may be thrown on the possible

TABLE III.—*Incidence of Alleged Causal Factors*

Aetiological Factor	Males	Females	Total
No known associated circumstances	50	50	100
Acute respiratory infection (bronchitis, pneumonia, measles, pertussis, etc.)	57	57	114
Psychological "shock" or "worry"	6	8	14
Pregnancy		10	10
Menstruation		5	5
Irritating fumes or dust	7	6	13
Excessive exertion	7	2	9
Miscellaneous causes (food, change of locality, or change of climate)			11

association of allergic tendencies and the nature of the aetiological factors by the data in Table IV, which compares the incidence of positive family histories (F.H.+), skin-test positives (S.T.+), and histories of previous allergic manifestations (P.A.M.) in the four largest aetiological

TABLE IV.—*Incidence of the "Allergic" Features in the Four Principal Aetiological Groups. The Actual Number of Patients in each Group is Shown in Parentheses*

	Aetiological Factors			
	Not Known	Respiratory Infection	Psychological	Pregnancy and Menstruation
F.H.+	50% (97)	55·5% (108)	57% (14)	28·4% (14)
S.T.+	36% (80)	27·4% (73)	36% (9)	12·5% (8)
P.A.M.	36·4% (89)	35·5% (93)	36% (9)	45% (11)

groups. These figures show that, although there is very little difference between the respective incidence of these allergic factors in the first three aetiological groups, in the fourth (pregnancy and menstruation) group the incidence of F.H.+ and S.T.+ is strikingly less, but that of other allergic manifestations somewhat increased. While the figures are too small to warrant definite conclusions, this would add further support to a hypothesis that "menstruation asthma" is truly allergic in origin in a high proportion of cases. The low positive-skin-test incidence would then be explained by the absence of hormonal extracts from the test series, and the low family incidence by the "sex-linked" nature of the allergy, which would be expected to reduce the family incidence of the manifestations to females only.

Aggravating Factors

An attempt was made to compare factors associated with the onset of individual attacks of asthma with those believed to have been concerned in the aetiology of the condition. The results are shown in Table V. These figures

TABLE V.—*Incidence of Aggravation by Certain Factors, Grouped According to Aetiology. The Actual Numbers of Patients in Each Subgroup are Indicated in Parentheses*

Aggravating Factors	Aetiological Factors				
	Unknown	Respiratory Infection	Pregnancy and Menstruation	"Dust"	Psychological Trauma
Respiratory infections	14·3% (85)	14·4% (91)	0 (12)	0 (13)	25·0% (12)
Food	34·1% (85)	32·2% (91)	16·7% (12)	15·4% (13)	33·3% (12)
Psychological disturbances	25·0% (85)	25·5% (91)	18·3% (12)	0 (13)	66·7% (12)
Pregnancy and menstruation	28·7% (40)	59·4% (45)	83·3% (12)	66·7% (6)	29·4% (12)
"Dust"	22·4% (85)	21·1% (91)	25·0% (12)	92·4% (13)	16·7% (12)
Climate	70·6% (85)	55·5% (91)	33·3% (12)	53·9% (13)	50·0% (12)
Exertion	35·3% (85)	37·0% (91)	41·5% (12)	15·4% (13)	16·7% (12)

show that three out of the four known aetiological factors also aggravate the asthmatic condition in a high percentage of patients. These are, pregnancy and menstruation (aggravated in 83.3%), "dust" (92.4%), and psychological disturbances (66.7%). Respiratory infections, on the other hand, differ markedly in that in only 14.4% of patients was the asthma aggravated by further respiratory infections. Thus it would appear that, while acute respiratory infections have initiated asthma so often that their association is unlikely to be fortuitous, subsequent attacks of asthma are surprisingly seldom occasioned by recurrences of respiratory infection. This might perhaps be explained on the assumption that the respiratory centre, or some other portion of the mechanism governing the tone of bronchiolar muscle, may have received a non-specific sensitization from the original infection which has facilitated an "asthmogenic" response to other stimuli, and may, in fact, establish the "asthma diathesis."

The relationships of aetiological to exacerbating factors may be summarized provisionally by their classification as follows:

Class A.—Factors which initiate the asthmatic condition and exacerbate asthma in a high proportion of cases. These are pregnancy and menstruation, "house dust," pollens, and psychological disturbances.

Class B.—Factors which are apparently associated with the aetiology of the asthma, but not with its subsequent aggravation, such as acute respiratory infection.

Class C.—Factors which frequently aggravate asthmatic attacks, but seldom seem to have played a part in the aetiology of the condition. These are food sensitivity, climatic conditions, and exertion. Together with dust and emotional upsets, such stimuli are well-known aggravators of any respiratory disturbances, particularly cough and dyspnoea.

Clinical and Other Findings in Cases of Asthma

No obvious abnormality was found on clinical examination in 122 out of 251 patients. As might be expected, where physical signs were present the vast majority of patients showed rhonchi. Obvious emphysema was found in 15 patients in this series. Only five of the patients had gross chest deformity (pigeon-breast, kyphosis, or "sunken chest"), the onset of asthma occurring in early life in four of them.

Radiologically, out of 196 patients whose films were available, 66 showed some abnormality—50 had chronic inflammatory changes only, four had old healed tuberculosis.

one active tuberculosis, four pulmonary fibrosis, three emphysema, two pleural thickening, and two cardiac dilatation.

Of 260 patients in whom the upper respiratory tract had been examined, no abnormality of nose, throat, or sinuses was found in 120. Of the rest, 66 had inflammatory lesions of the sinuses, throat, or nose, and 74 showed evidence of changes attributable to allergy only, such as vasomotor rhinitis, simple mucosal oedema, or polyp formation.

Progress

A questionary was circulated to 150 patients who had attended the asthma clinic between 1935 and 1940. Of these, 64 replied; their general progress is shown in Table VI.

TABLE VI.—*Results as Compiled from a Questionary*

Result	Males	Females	Total
"Cured" (i.e., no attacks for at least one year)	7	5	12
Died	7	4	11
Improved	13	9	22
Unchanged	4	2	6
Worse	4	9	13

Recoveries.—In the 12 instances of recovery the condition resolved suddenly in six, and gradually in the remainder. The mean duration of asthma in these cases was nine years. The alleged causes of cessation of the attacks are shown in Table VII. In two patients recovery was attributed to more than one cause.

TABLE VII.—*Alleged Causes of Recovery*

Causes	No.	Ages at Onset	Duration
"Grew out of the asthma"	3	15, 2, 3 years	2, 10, 11 years
Change of environment (war evacuation)	3	2, 2, 1 year	8, 14, 12 „
Cautery of nose	2	21, 48 years	23, 10 years
Specific protein desensitization	1	25 years	8 years
Tonsillectomy	1	2 „	8 „
Breathing exercises	1	2 „	14 „
Senility	1	57 „	24 „
Unknown	2	44, 29 years	10, 8 years

Eight of the above 12 patients therefore seem to have recovered without any active therapy, six of these being children. Analysis did not reveal any correlation between age of onset of asthma and ultimate prognosis.

Remedies Found Effective in Attacks.—From the nature of the information received from patients no accurate account could be compiled of the details of treatment found most helpful. It is of interest, however, to find that among the patients who did give a reasonably clear answer the use of one or more proprietary inhalants was considered to have been more effective than medicine from a bottle or than ephedrine tablets.

Discussion

From the above results several points emerge. First, there is support for the accepted view that most cases of asthma are of allergic origin, differences being dependent more upon variations in the nature of the allergic stimuli and their mode of action than upon departure from the allergic process. Secondly, the evidence implicating hormonal activity in the production of asthma is strongly suggestive and lends support to more conclusive findings by other workers regarding the allergic nature of this association (Zondek and Bromberg, 1947).

Clinical abnormalities in the chest (apart from wheezing) were remarkably few, and more interesting still was the rarity of any gross deformity of the chest, particularly when it is considered that in approximately 30% of this group of patients the asthma began in the first decade of life.

Unfortunately our records are not informative enough to enable conclusions to be drawn on the efficacy or otherwise of treatment of nasal sinuses or tonsillar abnormalities in relation to asthma. These conditions appear to fall into two main categories. The first, occurring in 25% of patients, consist of oedema of the nasal mucosa, polyp formation, and other non-inflammatory conditions, which are all possibly of allergic origin, and therefore probably symptomatic of the allergic state of which asthma is but another manifestation (Rackemann, 1937). The second group, including true sinusitis, infected tonsils, and chronic (infective) nasal catarrh, occurred in about 28% of all cases of asthma, and may be aetiologically significant. Although the results of active treatment of upper respiratory diseases has generally been found disappointing (Witts, 1934), it is possible that better results might follow treatment if it were confined to those in the latter group.

Mortality and Morbidity.—This series of cases is spread over a period of between seven and twelve years. It would therefore not be of value to compare the mortality here with that of groups observed over a much shorter period (e.g., Coke, 1927). An adequate follow-up of hospital patients is not always possible, for many drift elsewhere, and others for various reasons do not reply to letters. Of the 64 patients of whom later information was obtained 11 had died within the period—a somewhat surprising mortality of 17.2%; three had developed phthisis in the course of their asthma and died of the disease; three died as a direct result of their asthmatic attacks, and three others died of secondary cardiac failure. That asthma is potentially a fatal disease is too often overlooked, and the above figures underline the importance of long-term treatment in an attempt to safeguard the patient's future. While it is true that the patient must "learn to live with his asthma," it is clear that life would be both happier and longer in its absence.

Summary and Conclusions

Clinical and other findings in 294 cases of asthma have been examined with the object of analysing the natural history of the disease, its aetiology, and its prognosis. Evidence was obtained of the importance of the allergic factor, particularly of the relevance of hormonal allergy in the production of asthma in women. Comparison of the incidence of aetiological factors relative to those aggravating the condition suggests that the factors involved in the production of the asthmatic state may be of three kinds: aetiological and aggravating, aetiological but not aggravating, and aggravating but not apparently connected with aetiology.

From a relatively small series of cases which were followed up over a period of seven to twelve years, 19.4% had apparently fully recovered, while 17.2% had died. This mortality rate, though occurring in a series too small to warrant statistical analysis, nevertheless suggests that asthma as a potentially fatal disease has received rather less attention than it deserves.

We are particularly indebted to our former teacher and chief, Dr. Robert Coope, both for his permission to use the records of the Liverpool Royal Infirmary Asthma Clinic and for his kindly advice and helpful criticism during the production of this paper.

References

Coke, F. (1927). *British Medical Journal*, **1**, 955.
Pearson, R. S. B. (1934). Asthma Research Council Report. Quoted in *Lancet*, 1934, **2**, 1171.
Rackemann, F. M. (1937). *Proc. R. Soc. Med.*, **31**, 529.
Vaughan, W. T. (1933). *J. Lab. clin. Med.*, **19**, 53.
Witts, L. J. (1934). *Lancet*, **1**, 275.
Zondek, B., and Bromberg, Y. M. (1947). *J. Obstet. Gynaec. Brit. Emp.*, **54**, 1.

ANTIHISTAMINES IN BRONCHIAL ASTHMA

BY

HERBERT HERXHEIMER, L.R.C.P.&S.Ed. L.R.F.P.S.Glas.

(From the Surgical Unit and Chest Department, University College Hospital, London)

The beneficial action of antihistamines in hay-fever, perennial rhinitis, and urticaria is undisputed, but their use in human asthma has been doubted. In this paper experimental and clinical evidence is presented that the antihistamines are of considerable value in the treatment of this condition.

Experimental Evidence

Method

Bronchial spasm was induced in normal and asthmatic subjects by the aerosol inhalation of spasmogenic substances. This method avoided the risk connected with their parenteral injection in asthmatic subjects, whose response varies so widely; furthermore, their local application imitates the natural conditions more closely and avoids the danger of producing a strong general reaction.

The aerosol was produced by a pressure pump (kindly supplied by Messrs. Aerosols, Ltd.) to which a series of commercial nebulizers were attached. The unit was incorporated in the inspiratory part of the breathing circuit of a recording spirometer (Herxheimer, 1949a). The efficiency of the aerosol so produced can be judged from the fact that when isopropylnoradrenaline was inhaled a 0.25% solution produced similar effects in the same time as a 1% solution administered by a hand-operated inhaler.

As the amount of any drug inhaled cannot be determined accurately, the time of administration was counted in seconds. The degree of bronchial spasm was estimated by measuring the vital capacity, to which it was directly related (Curry, 1946). The maximum breathing capacity cannot be used as a test, as the overbreathing has in many cases a direct influence on the degree of spasm. Other tests which are based on the time required for full expiration do not seem to present any advantage. It is believed that the determination of the vital capacity is fully reliable provided that the thoracic cage is mobile and that there is no venous congestion.

The vital capacity was determined three times before each experiment and the mean was taken as the base-line. Subjects who could not produce three vital capacities within a range of 150 c.cm. were excluded. The spasmogenic substances used were 3% histamine acid phosphate, 2.5% acetyl-β-methylcholine chloride, and allergenic extracts of mixed pollen and of mixed inhalants, made extra strong for this purpose by Bencard's. For the relief of spasm isopropylnoradrenaline was used in 0.25% to 1% solution, pyribenzamine in 1.5% and other concentrations, and sometimes ephedrine and "chlorothen." In all cases one drop of glycerin was added to 2 ml. of the solution, except in the case of acetyl-β-methylcholine chloride, which was dissolved in propylene glycol. If bronchial spasm so produced did not subside spontaneously an antispasmodic was given after some time and immediate relief obtained. In other experiments with the same subjects an antihistamine substance was given beforehand orally or, in a few cases, as an aerosol, and the spasmogenic aerosol inhaled for the same time as before.

In a number of control experiments with the same subjects various substances were inhaled as aerosols—physiological saline, allergenic extracts, ephedrine in various concentrations, 10% ammonium chloride, aminophylline, and some antihistamines. Saline and ephedrine in low concentrations and ammonium chloride produced no effect, but high concentrations of ephedrine, pyribenzamine, and amethocaine caused reduction of vital capacity and wheezing in asthmatic subjects. In a number of patients genuine asthma was treated in the same way as induced asthma, and in some an antihistamine was given intravenously.

Results

Normal Subjects.—The inhalation of histamine in most cases caused subjective symptoms during the third minute, consisting of redness of the face, sometimes a headache, and a sense of constriction of the chest. Of the 16 subjects three showed no decrease of vital capacity. In two of these higher concentrations of histamine were tried. One showed a decrease after 10% histamine phosphate had been breathed for four minutes; the other showed no decrease. Of the remaining 13 subjects five showed reductions of between 5 and 9% and eight between 12 and 26%. The inhalation of acetyl-β-methylcholine chloride caused fewer and milder general symptoms. In only two cases out of 14 was the vital capacity decreased. This difference may be entirely due to the arbitrarily chosen amounts of aerosol administered. For instance, in one subject the vital capacity decreased after three minutes of inhalation from 4,000 to 3,600 c.cm. with mild general symptoms. After four

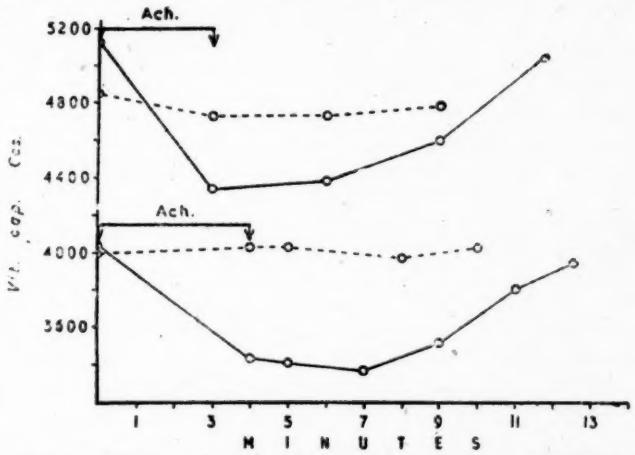


FIG. 1.—Change of vital capacity (as a measure of bronchial obstruction) in two normal subjects who inhaled acetyl-β-methylcholine chloride (Ach.) for three and four minutes. The interrupted lines show the same experiment after 25 and 50 mg. of phenergan had been given beforehand.

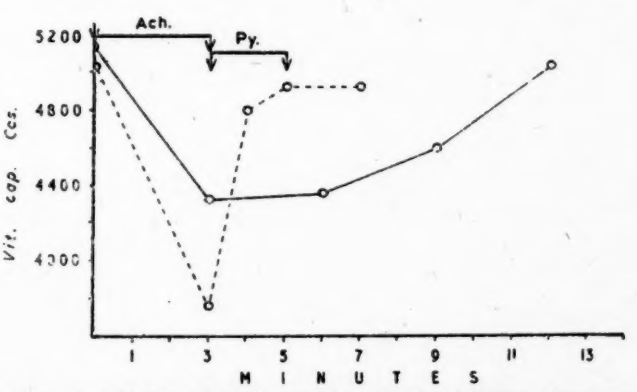


FIG. 2.—Change of vital capacity, representing the degree of bronchial obstruction in a normal subject after inhaling acetyl-β-methylcholine chloride for three minutes (uninterrupted line) and the same when inhaling pyribenzamine (Py.) 1.5% immediately afterwards for two minutes (broken line).

minutes' inhalation the symptoms were more severe, and the vital capacity decreased to 3,360 c.cm. When "phenergan" ("R.P. 3277") was given 90–120 minutes before the experiment the general symptoms were suppressed or reduced to a minimum. The vital capacity did not change. This was the case after histamine as well as after acetyl-β-methylcholine chloride (Fig. 1). In one case the inhalation of 1.5% pyribenzamine, given immediately after the acetyl-β-methylcholine chloride had depressed the vital capacity, very quickly restored it to its normal value (Fig. 2).

Cases of Induced Asthma.—The induction of bronchial spasm—the asthmatic attack—in patients involves some risk, as a very small amount of inhalant may cause a severe attack. In a patient whose reaction to a substance is unknown it is advisable to start with one whiff of the inhalant only and to await the reaction. With histamine and acetyl-β-methylcholine chloride this reaction usually appears at once in full strength. The patient feels tightness of the chest, and when he attempts to breathe out deeply he encounters difficulty not felt before. With allergenic extracts, especially when a very small amount produces a reaction, this difficulty in breathing—the "wheeze" which also indicates a decrease of vital capacity—often does not appear at once. Only a mild tickle or soreness is felt in the throat or in some related region (for instance, the shoulder), and the wheeze develops gradually two to five minutes later.

The protection against attacks induced in this way required more antihistamine than in normal subjects—phenergan was mostly used—and if the induced attack was severe—if, for instance, the vital capacity was reduced by about one-half—no protective effect could be obtained even with 75 mg. of phenergan. If, however, the amount of inhalant was just small enough to induce a mild attack, phenergan or "anthisan" ("neoantergan") suppressed it either completely or at least partly (Figs. 3 and 4). Pyribenzamine as aerosol was effective in partially relieving the induced spasm in some cases, but not in others.

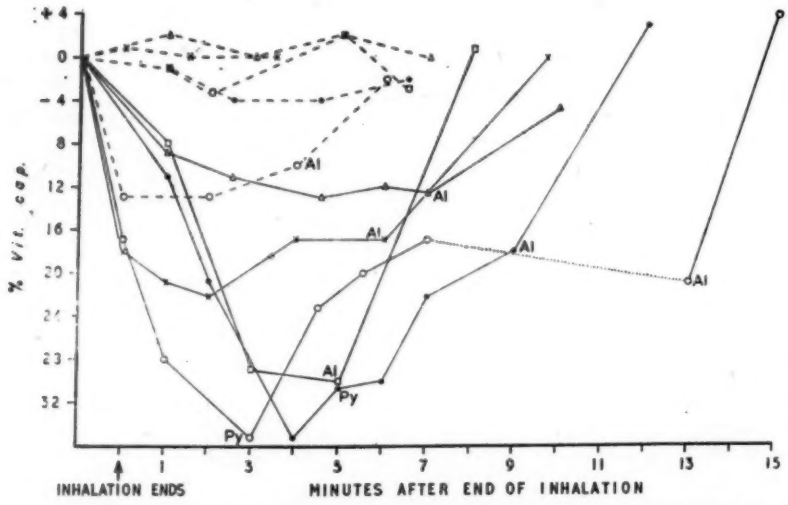


FIG. 3.—Protective action of antihistamines against bronchial obstruction caused by acetyl-methylcholine chloride inhalation. Five subjects. *Full lines* = Change in vital capacity after inhalation without protection. *Interrupted lines* = Change in vital capacity after varying doses of antihistamine had been given beforehand.

Period of inhalation		Dosage of antihistamine	
△	90 sec.	62.5	mg. phenergan
×	180 ,,	500	mg. anthisan
○	60 ,,	50	mg. phenergan
□	12 ,,	50	mg. ,,
●	35 ,,	75	mg. ,,

Py. Al. = Pyribenzamine 1.5% or aleudrine 1% inhaled in order to terminate the asthmatic attack.

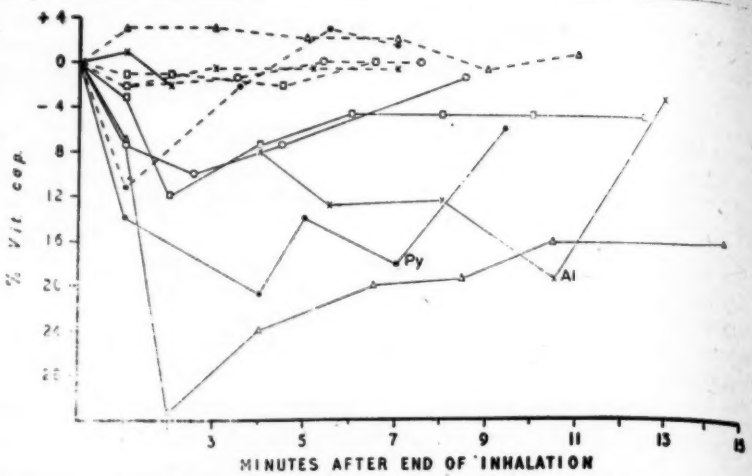


FIG. 4.—Protective action by antihistamines against bronchial asthma induced by mixed pollen inhalation. Five subjects. *Full lines* = Change in vital capacity after inhalation without protection. *Interrupted lines* = Change in vital capacity after varying doses of phenergan had been given beforehand.

Period of inhalation		Dosage of phenergan
△	45 sec.	37.5 mg.
×	5 ,,	25.0 mg.
○	30 ,,	37.5 mg.
□	25 ,,	37.5 mg.
●	180 ,,	50.0 mg.

Py. Al. = Pyribenzamine 1.5% or aleudrine 1% inhaled in order to terminate the asthmatic attack.

Cases of Genuine Asthma.—Pyribenzamine aerosol frequently relieved bronchial spasm. As shown in Table I, in 12 patients the vital capacity was increased by over 200 c.cm. after inhalation of this drug. There were 12 other patients in the group, five of them elderly and sufferers from emphysema, in whom the increase was absent or negligible. Intravenous anthisan often produced marked relief, but the substance must be injected very slowly to avoid vomiting and circulatory collapse (Table II). Three cases in which no increase of vital capacity was obtained are not included in the table. Phenergan injected intravenously had also a beneficial effect (Fig. 5).

Clinical Evidence

The spontaneous and rapid changes in the asthmatic condition and the psychological factors which are almost always involved in the aetiology necessitated certain precautions in the selection of patients. Those who showed rapid fluctuations and those with long free intervals were excluded. This left the patients with moderate or mild attacks which occurred frequently and those who were in an asthmatic state.* Of these, only patients were selected who had a long experience of the disease and had tried many remedies, often without success, and thus appeared not unduly prone to suggestion. They had been known to the observer for some time; their reaction to various drugs had been investigated and their seasonal

*The term "asthmatic state" is used in this paper for bronchial spasm continuously present for long periods whether mild, moderate or severe.

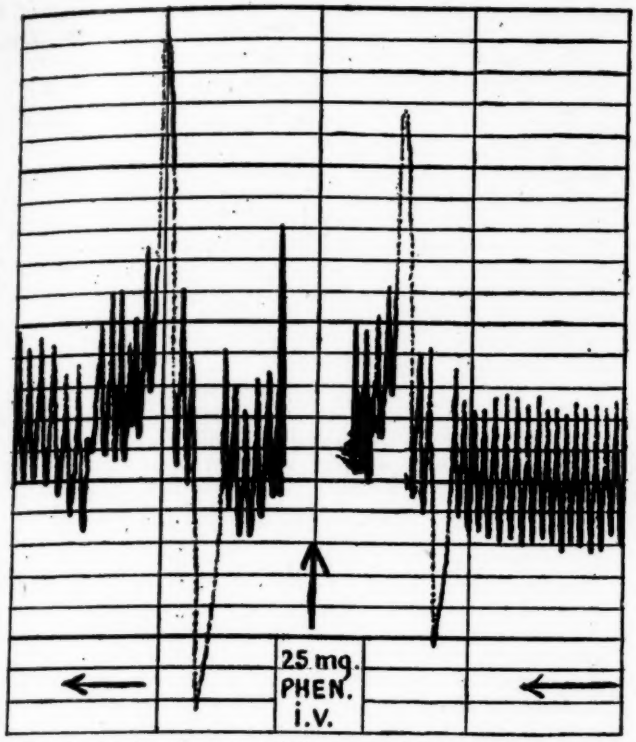


FIG. 5.—Asthmatic state. Vital capacity before (1,700 c.cm.) and 15 minutes after (2,240 c.cm.) intravenous injection of 25 mg. of phenergan.

TABLE I.—*Effect of Pyribenzamine Aerosol in Genuine Asthma*

Case No.	Highest Vital Capacity Ever Recorded	Vital Capacity Before Inhalation	Vital Capacity After Inhalation	Strength of Aerosol (%)
1	3,015	1,620	2,260	5
2	2,960	1,860	2,240	5
3	2,995	1,550	2,190	5
		2,000	2,300	5
		1,680	1,940	1
		2,100	2,650	1
4	2,980	2,290	2,520	5
5	3,900	3,420	3,900	5
6	2,560	2,325	2,550	1
7	2,540	2,330	2,540	1
8	3,690	2,550	3,060	1
9	3,500	2,700	2,960	1
		2,770	3,405	1
10	3,460	2,740	3,300	1·5
11	5,180	3,270	4,100	1·5
12	3,670	1,640	2,200	1·5

The 5% inhalation was carried out by hand nebulizer, the 1% and 1·5% inhalation by air-pressure pump.

TABLE II.—*Effect of Anthisan and Phenergan Given Intravenously in Genuine and in Induced Asthma*

Case No.	Highest Vital Capacity Ever Recorded	Vital Capacity		Amount of Anthisan Given	Remarks
		Before Injection	After Injection		
1	3,015	1,870	2,200	50 mg.	Genuine asthma
2	2,960	2,360	2,620	50 mg.	"
3	2,995	1,900	2,190	40 mg.	"
		2,655	2,805	50 mg.	"
13	5,300	3,785	4,005	50 mg.	"
14	4,440	1,690	2,190	100 mg.	"
15	4,260	1,620	2,600	100 mg.	"
16	2,935	1,980	2,230	50 mg.	"
17	2,640	2,195	2,360	50 mg.	"
18	2,430	1,470	1,790	75 mg.	"
19	1,760	1,470	1,700	100 mg.	"
		1,300	1,640	100 mg.	"
1	3,015	1,690	2,070	50 mg.	Induced by mixed inhalants
13	5,300	3,340	4,080	50 mg.	Induced by mixed pollen
		4,240	5,250	50 mg.	" "
20	5,510	3,860	4,510	100 mg. Phenergan	" "
1	3,015	1,710	2,230	25 mg.	Genuine asthma
3	2,990	1,760	2,170	25 mg.	" "
26	2,910	2,145	2,505	25 mg.	" "

variations were known. Their remedies were changed periodically, sometimes to placebos. These precautions made large-scale controlled experiments with dummy tablets unnecessary, in my opinion. The severity of the individual complaint was conveniently indicated by the number of aerosol inhalations required each day. The aerosol usually contained papaverine, atropine, and either adrenaline or isopropylnoradrenaline. The patients were asked to use their hand inhaler only when the wheeze became intolerable. As a rule they had to inhale on waking and at bedtime, but often four or six inhalations were taken during one night. The reduction in the number of inhalations required was regarded as an indication of the efficacy of an antihistamine substance.

The antihistamines used were mainly anthisan (100–600 mg.), phenergan (25–100 mg.), and "benadryl" (50–250 mg.). These doses were always given at bedtime, as their soporific effect is too great to allow their use during the day. These patients were therefore in need of an antispasmodic in the daytime, and ephedrine was usually given in its optimum amount on waking and after lunch. This combination proved very useful, because ephedrine interferes with sleep and could not be given at bedtime, and two daily doses of it do not cause tolerance. For those intercurrent superimposed attacks not suppressed by antihistamine and ephedrine, isopropylnoradrenaline ("aleudrine") was used either by inhalation or perlingually.

Twenty-six patients improved after receiving anthisan and ephedrine. Thirty-one were given anthisan and phenergan on alternate nights and ephedrine in the daytime, 11 received phenergan and ephedrine, two had phenergan alone, four had anthisan alone, five had benadryl and ephedrine, and two were prescribed benadryl only. All these patients showed definite improvement in the number of inhalations and in their physical efficiency. Three patients with severe chronic asthma and six with mild or moderate chronic asthma obtained no beneficial effects from any of the antihistamines. In others the effect of these drugs could not be assessed because of sudden changes in the character of the disease.

It should be noted that not all of the patients on anthisan reacted well to phenergan, or vice versa, although many of them did. Some of those who did not respond to either were found to respond to benadryl. In no case did we succeed in influencing an acute attack by an oral dose of antihistamine. Night attacks were suppressed only if they were mild attacks superimposed on a moderate asthmatic state, but not if they occurred as comparatively violent spasms after a free interval, frequently seen in the juvenile type of asthma.

Small doses which are satisfactory in hay-fever, urticaria, and perennial rhinitis were not sufficient in the treatment of asthma. The effective evening dose of anthisan was found to be 300–500 mg. and that of phenergan 50–75 mg. Benadryl, in the few cases in which it was effective, was active in small amounts—50–100 mg. Pyribenzamine was not tried; chlorothen and "histadyl" had no definite effects.

The side-effects of the antihistamine drugs varied with the dosage. Both anthisan and phenergan caused drowsiness, which was of longer duration with the latter agent. The action of phenergan was often evident after 12 hours or longer, and its antiasthmatic effect in the early morning after an evening dose was highly desirable. On rare occasions, however, these drugs caused sleeplessness. This effect was particularly noticeable with phenergan, and appears to be more pronounced if an overdose is given. A most undesirable side-effect is the nausea that is often caused by anthisan. This drug should always be taken with food.

No clinical signs were found to discriminate between patients who would or would not be responsive to antihistamines. On the whole I think—and this is not more than an impression—that patients with asthma of extrinsic origin responded more easily, and those in whom the bronchial spasm had developed subsequent to emphysema, less. Young subjects tend to respond more favourably than older persons.

Case Reports

The following are extracts of some representative case histories:

Case 21.—Woman aged 30, October 15, 1948. Asthma since 5 years old. Has been waking up three to four times a night during the last nine months, and has had to inhale a papaverine–atropine mixture which gave relief. Increasingly breathless on exertion; thorax emphysematous; unable to do her work; rhonchi ++. Treatment: anthisan 0.3 g. and phenobarbitone ½ gr. (32 mg.) at bedtime; ephedrine ¾ gr. (50 mg.), later 1¼ gr. (81 mg.), morning and after lunch; "theamin" mid-morning. October 22: Very fair, hardly needed inhaler; breathing exercises started. February 11, 1949: She is occasionally a little breathless on exertion and has then to make use of her inhaler, but she has been very well and fit for her work.

Case 22.—Man aged 36, July 16, 1948. Had nocturnal attacks for three years, which became more frequent when he moved from Southampton to London. He was wheezy during both night and day, and could not sleep much because of breathlessness. Ephedrine previously gave relief, but is now ineffective. On examination: chest barrel-shaped, rhonchi +++, vital capacity 2,980 c.cm. (reduced by about 33%). Treatment: anthisan 0.4 g. at bedtime with phenobarbitone ½ gr. (32 mg.); ephedrine 1½ gr. (97 mg.), later 2 gr. (130 mg.), morning and after lunch. July 23: Much better. No attacks during the night, although he wakes up for short periods. Can move about more easily; sputum much decreased. November 12: Has been very well; only one attack in four months. A little wheezy during fog. March 11, 1949: Unchanged. Vital capacity 4,520 c.cm.

Case 23.—Man aged 22, May 28, 1948. Asthma since the age of 3. Frequent coughs and colds every winter. May be free from wheezing for two to three weeks only. During summer, hay-fever and asthma. "Felsol," ephedrine, and the inhalation of a papaverine–atropine mixture give temporary relief; inhales three times during the day, three times during the night. On examination: chest deformed, kyphosis, rhonchi ++. Treatment: anthisan 0.5 g., plus 1 gr. phenobarbitone (65 mg.) at bedtime, ephedrine 1½ gr. (97 mg.) morning and after lunch; neb. aleudrine 2% for inhalation. August 27: Does not require treatment during the night, but is still wheezy on waking, and then has to make use of his inhaler, but he does not need it during the day. December 10: Has remained well except for one setback caused by an infectious cold, but has now become intolerant to anthisan (diarrhoea and vomiting). Benadryl 200 mg. substituted, but the nocturnal attacks recurred; phenergan 75 mg. permitted the patient to sleep through till 5.30 or 6 a.m., when he had to use the inhaler. No inhalations required during the day. Since then he has been able to complete his training as a bookbinder.

Case 10.—Woman aged 25, May 21, 1948. Asthma since the age of 2½; hay-fever since 10. Asthma worse during the last 10 years. Attacks last from two to four weeks. There may be free intervals of six months or more, but the intervals are not completely free from wheezing. Summer usually worse than winter. Sensitive to small doses of ephedrine. On examination: no signs of emphysema; few expiratory rhonchi; vital capacity normal (3,400 c.cm.). Treatment: anthisan 0.15 g.; later phenergan 25 mg. at bedtime, ephedrine ¼ gr. (16 mg.) morning and midday. Later the ephedrine was replaced by methylephedrine 2/3 gr. (45 mg.). February 25, 1949: Very well. Occasional mild attacks easily checked by aleudrine perlingually.

Case 26.—Man aged 34, August 6, 1948. Asthma since the age of 8. Until six months ago attacks occurred every night and occasionally during the day. They then increased in frequency, but were relieved by the inhalation of a papaverine–atropine mixture. Five weeks ago a severe attack made injections of adrenaline necessary. Has not been free from wheezing since; inhales twice during the night, three times during the day, and needs 5–10 minims (0.3–0.6 ml.) of adrenaline daily. On examination: barrel chest, kyphosis; vital capacity 3,150 c.cm.; rhonchi +++. Treatment: anthisan 0.5 g. at bedtime, which reduced the nocturnal attacks to one. Later, ephedrine 2½ gr. (162 mg.) was given on alternate days, and 75 mg. of phenergan every other night instead of anthisan. Under this regime the patient could sleep through till 5 or 6 a.m., when he had to use his inhaler. Phenergan usually enabled him to sleep about an hour longer than did anthisan. In daytime he had to inhale three to four times, but he did not need adrenaline, and he can now move about without restriction and look after his business.

Case 24.—Woman aged 53, October 1, 1948. Asthmatic attacks for 15 years. For the last three months had frequent attacks, provoked by mild exertion and during the night. Ephedrine ½ gr. (32 mg.) and inhalations of a papaverine–atropine mixture give temporary relief. Believes that her present work with wool caused the deterioration. On examination: chest barrel-shaped, rhonchi +++, vital capacity 1,700 c.cm. Treatment: anthisan 0.3 g., with phenobarbitone ½ gr. (32 mg.) at bedtime and ephedrine 1 gr. (65 mg.) twice in the day, did not have any effect; benadryl 150 mg. plus phenobarbitone 1 gr. (65 mg.) at bedtime improved the condition at night so much that after a week only one inhalation was needed instead of five. Her condition during the day was equally improved by ephedrine 2 gr. (130 mg.) in the morning and after lunch. Breathing exercises were now started. January 28, 1949: Very well; seldom required inhalation. March 11: Well, apart from a transient cold and cough. Sleeps well, is able to move about freely and to do her work. Vital capacity now 2,670 c.cm.

Further case histories are published elsewhere (Herxheimer, 1949b).

Discussion

The evidence that antihistamines have any action against bronchial spasm has so far been received with scepticism. It had been shown experimentally that they counteracted bronchial spasm induced by histamine in animals and man (Curry, 1946). Schiller and Lowell (1947) and Curry and Lowell (1948) could not find a protective effect when the bronchial spasm was induced by mecholyl or by the inhalation of allergenic extracts. Unfortunately, they used the weaker antihistamines (benadryl and pyribenzamine) in small amounts, and tried them on a few patients only. From these negative results it appeared as if the histamine-induced bronchospasm were a spasm *sui generis* and had nothing in common with other types of bronchial spasm—for example, that induced by acetylcholine or the spasm of genuine asthma. From the present experiments with induced bronchospasm it is not possible to distinguish different types, except that they develop with different speed.

The strongest antihistamines, if used in sufficient dosage, are able to suppress induced bronchial obstruction if it is mild—e.g., if it does not depress the vital capacity by more than approximately 30%. If a severe attack is induced the protection becomes partial or fails altogether. This is in accord with clinical experience. I have never seen an acute asthmatic attack influenced by an antihistamine. The failure to abolish any bronchial obstruction completely can also be seen if the effect of the antihistamines is compared with the effect of isopropylnoradrenaline, as seen in Figs. 3 and 4. When in some of these experiments pyribenzamine gave partial relief, aleudrine quickly restored the vital capacity to normal. This partial action may be comparable to the results of Bain (1949), who could not abolish the histamine effect on the skin completely with antihistamines.

It must be emphasized that the dosage of phenergan used in the induced attacks varied greatly—from 25 to 75 mg.—and that in one case I was not able to suppress a mild attack caused by acetyl-β-methylcholine chloride. Pyribenzamine used as aerosol had a definite effect in some cases but not in others. This confirms the experience that none of these substances is effective in every subject. Some patients are sensitive to one but not another, and so far it has not been possible to predict whether a given substance would be effective in a particular patient.

As the experimental evidence is definite it seems strange that some observers should have had negative clinical results (Hunter and Dunlop, 1948 ; Southwell, 1948 ; Dunlop and Hunter, 1948). Their method was not completely satisfactory, as I have pointed out before (Herxheimer, 1948b). The patients were unselected, and the dosage was uniform and rather low. Under such conditions a small proportion of successes may be expected, and it will not differ much from the pseudo-successes achieved by the natural vagaries of the disease and by suggestion.

I have described some effects of anthisan (1948a), and the North American literature contains numerous reports of so-called clinical successes. The percentage of cures reported is usually much smaller than in urticaria or hay-fever, and the assessment of clinical success is indefinite. Our clinical experience shows that the stronger antihistamines (and in some cases benadryl) have a beneficial effect on those patients who are sensitive to them. They do not help at all in severe attacks and in those acute attacks which develop after a long interval of freedom. They are excellent in the mild and moderate chronic asthmatic state (for instance, *after* acute attacks), although they do not abolish the disease completely.

Two criticisms of the present series must be considered. One is that the beneficial action of the antihistamines in asthma is due to their sedative influence. There is no doubt that these drugs have a sedative action, but it is distinct from their antispasmodic property. I have attempted to obtain the same anti-asthmatic effect with large doses of phenobarbitone, up to 2 and 3 gr. (130–195 mg.), but without success. The patient feels very tired, but is still awakened by the attacks. The soporific effect of anthisan and phenergan wears off to some measure after four or five days' use, but the antispasmodic effect persists. Some patients do not experience a soporific effect at all, and in spite of this the antispasmodic effect is present.

The other criticism is that the beneficial effect is due to suggestion. It is certain that asthmatic patients respond to suggestion more readily than normal persons. But in my patients many different drugs were tried in different dosages, and it usually happened that one particular dosage of one or two drugs was found effective, and any change to another substance or dosage was quickly followed by a relapse. When many attempts have been made at treatment the asthmatic patient is no longer deceived by suggestion. Even if many of the beneficial results were due to suggestion this could not be the explanation of the experiments with induced bronchoconstriction in normal and asthmatic subjects.

I have come to the conclusion that the antihistamines constitute a definite improvement in our treatment of some kinds of chronic asthma. They are the best agents we have for night-time administration, and, if they are combined with ephedrine in the daytime and aleudrine (isopropylnoradrenaline) or aminophyllin to cut short acute superimposed attacks, the success achieved is worth the laborious process of determining the optimum dosage, which may require weeks of patient observation. The practitioner may feel that this will be difficult ; but our experience is still very small, and it may well be that more effective substances and simpler ways of applying them will be found. In any case, it would be a grave error to add the antihistamines to the vast rubbish-heap of anti-asthmatic remedies which have been found wanting.

Summary

Phenergan and anthisan suppress mild bronchial spasm in humans induced by histamine, acetyl-β-methylcholine chloride, and allergenic extracts.

Severe attacks so induced could not be suppressed. There is no evidence that oral doses of these substances suppress acute severe attacks of genuine asthma.

Clinical evidence suggests that the stronger antihistamines are of great value in the mild and moderate asthmatic state, especially during the night. In this condition they can be conveniently combined with day doses of ephedrine and, if necessary, aleudrine in order to check acute exacerbations. The wide variation of the response makes it necessary to try out the antihistamine and its dosage individually.

References

Bain, W. A. (1949). *Proc. R. Soc. Med.* (in press).
Curry, J. J. (1946). *J. clin. Invest.*, **25**, 785, 792.
—— and Lowell, F. C. (1948). *J. Allergy*, **19**, 9.
Dunlop, D. M., and Hunter, R. B. (1948). *Lancet*, **1**, 849.
Herxheimer, H. (1948a). Ibid., **1**, 667.
—— (1948b). *British Medical Journal*, **1**, 999.
—— (1949a). *J. Physiol.*, **109**, 4P.
—— (1949b). *Ann. paediatr., Basel*, **172**, 333.
Hunter, R. B., and Dunlop, D. M. (1948). *Quart. J. Med.*, n.s. **17**, 271.
Schiller, I. W., and Lowell, F. C. (1947). *Ann. Allergy*, **5**, 564.
Southwell, N. (1948). *British Medical Journal*, **1**, 877.

A CASE OF TOXOPLASMOSIS*

BY

A. B. NUTT, M.B., B.S., M.Sc., F.R.C.S.
TREVOR WRIGHT, M.D., D.C.H.
J. H. BOWIE, M.B., Ch.B.

AND

C. P. BEATTIE, M.B., Ch.B., D.P.H.

(From the Children's Hospital, Sheffield, and the Bacteriology Department, University of Sheffield)

An annotation in the *British Medical Journal* of April 23, 1949 (p. 718), reviews toxoplasmosis and gives references to important contributions to our knowledge of this disease. A paper by Callahan, Russell, and Smith (1946) and Binkhorst's (1948) book may also be found useful by those interested in the subject. As is stated in the annotation, the first case of congenital toxoplasmosis recognized in this country was described by Jacoby and Sagorin (1948). At the time when their report was published we were investigating another case, which we now put on record.

Case Report

The patient, a girl aged 4, was born normally at full term ; weight 6 lb. 5 oz. (2.86 kg.) The neonatal period was uneventful—no jaundice, anaemia, haemorrhagic phenomena, or respiratory distress—and during the first year she was regarded by her mother as normal, having no illness, feeding difficulties, skin rashes, diarrhoea, or vomiting. At 18 months of age her parents noticed that she was partially blind and had a squint. She was clumsy in her gait and had a tendency to fall over objects placed in her way. Apart from this she was in good health

*Read in the Section of Ophthalmology at the Annual Meeting of the British Medical Association, Harrogate, 1949, by Mr. A. B. Nutt.

and was able to walk and play and to pick up objects when she dropped them.

Her mother, father, sister, aged 5, and brother, aged 2, are alive and well. No abnormality can be found in their eyes, and their mental development is normal. There is no history of tuberculosis or syphilis in the family. The mother has had three normal pregnancies and no miscarriages, and she has no recollection of any illness, even slight or transitory, during any of the pregnancies.

Because of her difficulty in seeing and her squint, the patient at 18 months was brought to see one of us (A. B. N.). Examination of the fundi at that time revealed a choroido-retinal scar involving each macula. She was kept under observation, but it was not until June, 1948, that the possibility of toxoplasmosis was considered on account of the clinical similarity of her condition to that of cases seen in Geneva with Professor Franceschetti and Dr. Bammatter.

On October 20 she was admitted to hospital for more complete investigation. At that time she weighed 37 lb. (16.78 kg.). Nothing of consequence was found in the general physical examination. The results obtained by cytological and biochemical examination of the blood, cerebrospinal fluid, and urine were within normal limits; the Wassermann reaction and the Kahn test on the blood were negative. Certainly, however, the child was mentally retarded.

The visual acuity could not be accurately determined; obviously it was low centrally, but it was good enough peripherally for the child to distinguish large objects. There was a left convergent strabismus and a searching nystagmus. The anterior segment of each eye was normal and the pupils reacted to light both directly and consensually, but the reaction was sluggish.

In the right eye there was slight pallor of the disk, but the retinal vessels were of normal calibre. There was a large oval macular scar measuring 4 D.D. horizontally and 2½ D.D. vertically (Fig. 1). The edges were fairly well defined. The inner half of the area showed choroido-retinal atrophy with little or no pigment, but in the outer half there was gross pigmentary

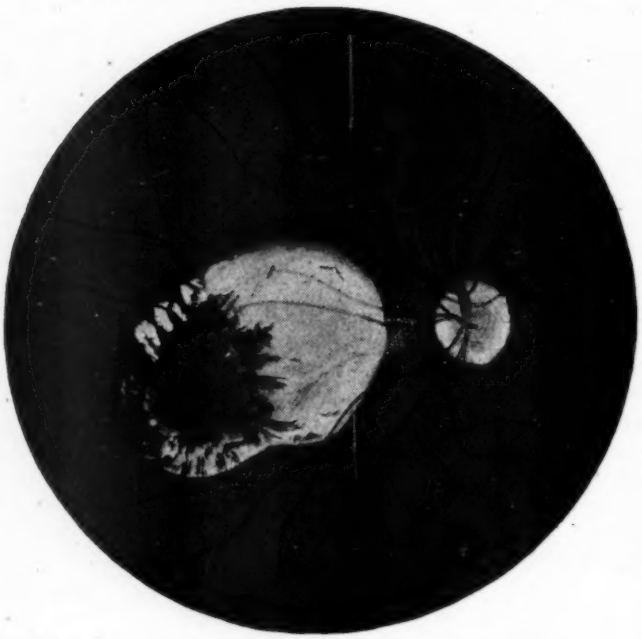


FIG. 1

disturbance surrounding an area in which choroidal vessels could be seen.

In the left eye there was an advanced degree of optic atrophy, with some attenuation of the retinal vessels. The temporal margin of the disk was obscured by a slightly elevated, possibly glial, mass, on the surface of which there was fine pigmentary disturbance. There was an extensive choroido-retinal scar (Fig. 2). It consisted of a central portion more or less circular in shape and approximately 2 D.D. across. This was joined to a larger and more temporal scar by a short, narrow isthmus of choroido-retinal atrophy traversed by a large choroidal vessel. The larger scar was triangular in shape, the sides being about equal in length, the apex pointing to the periphery in the

FIG. 2

horizontal meridian and the base towards the disk. Each side of the triangle measured about 3 D.D. The edges of the whole scar were sharply defined. The white sclera was widely exposed and a number of large choroidal vessels could be seen running across its base.

There was fairly gross pigmentary disturbance, especially in the temporal portion of the scar, and both showed connective-tissue proliferation.

Serology

The patient's cerebrospinal fluid was examined for toxoplasma, but without success. Sera from the patient and from other members of her family were then examined for the presence of toxoplasma-neutralizing antibodies by intradermal tests in rabbits as described by Sabin (1942). The first test, carried out with fresh serum from the patient (not shown in the following Table), indicated that it neutralized a 1:10,000 dilution. This Sabin interpreted as equivocal, and recommended that the test should be repeated. This was done, and sera from other members of the family were also tested, with the following results.

Subject	Age (Years)	Date of Test	Serum	Size of Skin Lesions produced by Dilutions of Toxoplasma Suspension Mixed with Serum Under Test			
				1:20	1:100	1:1,000	1:10,000
Patient	3¾	19/11/48	Fresh	+++	+++	+	0
Mother	27	,,	,,	+++	+++	++	0
Sister	5	,,	,,	+++	+++	+++	++
Father	36	14/1/49	,,	+++	+++	+++	++
,,	,,	21/1/49	Freeze-dried	+++	+++	++	+
Brother	2	14/1/49	Fresh	+++	+++	+++	+
,,	,,	21/1/49	Freeze-dried	+++	+++	+++	+
All controls	..	..	..	+++	+++	++	+

The accompanying Diagram shows the size of the skin lesions produced in the rabbit. Comparison of the control series (dilutions of toxoplasma suspension without serum) with the test series (dilutions of toxoplasma suspension to which was added serum from the patient) will show the extent to which her serum neutralized the toxoplasma. These results suggested the presence of toxoplasma antibody in the serum of the patient and her mother. Freeze-dried specimens of their sera and of the serum of the sister were sent to Dr. Sabin, who very kindly examined them by his dye-test method (Sabin and Feldman, 1948) and by the complement-fixation method. He reported as follows:

	Dye Test (Titre)	Complement-fixation Test (Titre)
Patient	1 : 1024	1 : 10
Mother	1 : 32	1 : 4
Sister	0	0

Sabin considered that these results supplied strong evidence that the disease from which the patient suffered was congenital toxoplasmosis. The titre in the mother he thought rather lower than is sometimes found four years after infection.

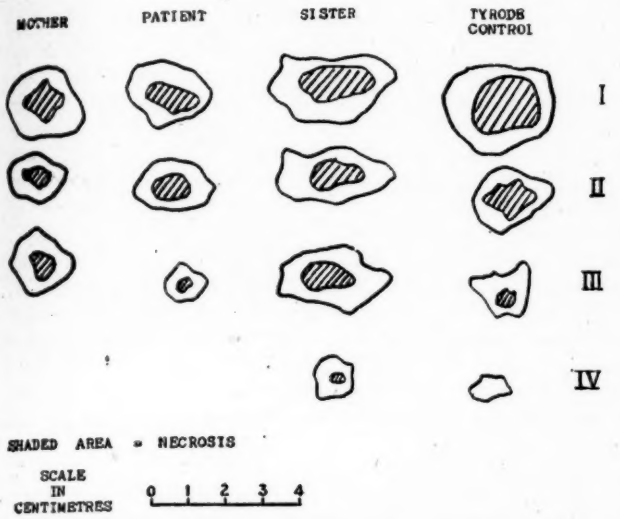


Diagram showing tracings of skin (rabbit) neutralizing test for toxoplasmosis. Final dilution of toxoplasma suspension I, 1 : 20; II, 1 : 100; III, 1 : 1,000; IV, 1 : 10,000.

Discussion

In 1942 a group of 151 cases was investigated by Sabin, employing the toxoplasma-neutralizing antibody test. He found that not only did the infants and children showing the now well-recognized tetrad (convulsions, internal hydrocephalus, intracerebral calcification, and choroidoretinitis) and their mothers give positive reactions for the toxoplasma, but so also did other varied types of case. These were mothers who had given birth to anencephalic monsters, older children and adults with chorioretinitis of unknown aetiology, some unexplained cases of encephalitis, and children and adults who had congenital cataract and other disturbances of the eyes. The above findings are quoted as a reminder that infection with the toxoplasma may produce a very varied clinical picture, including isolated disorders of the eye in which previously the aetiology was said to be obscure or simply congenital.

As regards the ocular findings in toxoplasmosis, Binkhorst (1948) found focal retinal lesions in all his cases, and he suggests that chorioretinitis may sometimes be the only clinical manifestation of this infection. He considers that for the clinical diagnosis of toxoplasmosis ophthalmoscopic examination is indispensable.

In 1942 Cowen, Wolf, and Paige reported six cases of toxoplasmosis, in all of which the outstanding features were ocular abnormalities such as chorioretinitis, microphthalmos, and strabismus. The ocular signs in toxoplasmosis have been carefully studied and recorded by Koch, Wolf, Cowen, and Paige (1943). The fundus lesions are predominantly bilateral, focal, and multiple. The macular region is invariably involved, and, less often, the periphery. The earliest change is localized oedema of the retina. The ultimate scar has a punched-out appearance, and there is extensive choroido-retinal degeneration together with connective tissue and pigment proliferation, the rest of the retina remaining normal in appearance during all observed stages of the infection. Optic atrophy seems to be the rule.

The case reported above was first brought for medical advice because the mother noticed the child's clumsy movements and suspected defective vision. To the mother the child appeared otherwise quite normal. It should be stressed that the main features of the case were ophthalmic in their presentation. It was only on closer examination and on watching the progress of the child that mental retardation was recognized. This latter is certainly more than could be attributed to defective vision.

Intracerebral calcification has been found post mortem or detected by radiography in most cases of congenital toxoplasmosis. The finding, however, does not seem to be specific or essential for the diagnosis, and this impression is confirmed by Binkhorst (1948), Adams *et al.* (1948), and Sabin (personal communication). The last-named, however, has had only one other case in which intracerebral calcification was absent.

Admittedly a diagnosis of toxoplasmosis is clinched only by isolation of the toxoplasma. At the same time it is felt that the clinical picture in this case, combined with the serological results, warrants the diagnosis of congenital toxoplasmosis. It is inferred that the infection was acquired *in utero* from the mother, as her serum gave a positive result in the neutralizing antibodies tests. An interesting point is that the patient's sister, aged 5, showed no evidence of antibodies, nor did the brother, aged 2. This suggests the possibility that the mother's infectivity may have been limited to a period within three years.

Summary

A case of congenital toxoplasmosis is described in a girl aged 4 years.

The main clinical features are defective vision with a searching nystagmus, bilateral chorioretinitis, and mental retardation.

Evidence in favour of the diagnosis is supported by the toxoplasma-neutralizing antibody test, the dye test, and the complement-fixation test.

Ophthalmoscopic examination would seem to be important for the clinical diagnosis of toxoplasmosis, and evidence of choroido-retinal disturbance should be looked for in all children with a history of convulsions, hydrocephalus, and mental retardation.

References

Adams, F. H., Adams, J. M., Kabler, P., and Cooney, M. (1948). *Pediatrics*, **2**, 511.
Binkhorst, C. D. (1948). *Toxoplasmosis*. Stenfert Kroese, Leiden.
British Medical Journal, 1949, **1**, 718.
Callahan, W. P., Russell, W. O., jun., and Smith, M. G. (1946). *Medicine*, **25**, 343.
Cowen, D., Wolf, A., and Paige, B. H. (1942). *Arch. Neurol. Psychiat., Chicago*, **48**, 689.
Jacoby, N. M., and Sagorin, L. (1948). *Lancet*, **2**, 926.
Koch, F. L. P., Wolf, A., Cowen, D., and Paige, B. H. (1943). *Arch. Ophthal., Chicago*, **29**, 1.
Sabin, A. B. (1942). *Proc. Soc. exp. Biol., N.Y.*, **51**, 6.
—— and Feldman, H. A. (1948). *Science*, **108**, 660.

In order to help build up the National Hospital Service Reserve, which will provide an organization of trained men and women in the event of war to meet the needs of expanded hospital services, the Ministry of Health has asked local authorities to provide at civil defence corps recruiting centres facilities for officers of the St. John Ambulance Brigade and the British Red Cross Society to recruit auxiliary members of the reserve.

CHLORAMPHENICOL IN TYPHOID FEVER

A PRELIMINARY REPORT OF CLINICAL TRIAL IN 6 CASES

BY

J. C. PATEL, M.D., Ph.D., M.R.C.P.
D. D. BANKER, M.D.

AND

C. J. MODI, M.B., B.S.

(*From King Edward Memorial Hospital, Bombay*)

Chloramphenicol (chloromycetin) is a new antibiotic derived from a soil streptomyces known as *Streptomyces venezuelae*. It was first isolated for therapeutic purposes by Ehrlich and his associates in 1947.

The first report of the beneficial effect of this antibiotic in typhoid fever came from Woodward and his co-workers in Malaya in 1948. Since then the drug has been given a trial by many workers in different parts of the world. Murgatroyd (1949) has tried it in one case in London. A controlled trial is in progress in the United Kingdom as a result of the recent Berkshire outbreak (Bradley, 1949). In India the drug has been tried in typhoid fever by Shah (1949) and by Vakil (1949).

The diagnosis of typhoid fever may be open to doubt in many of the cases of these two Indian authors. Shah's series of 33 cases contains only eight with positive blood cultures, and Vakil does not mention the number of cases in which blood culture was positive in his series of 14. Neither of these authors mentions previous T.A.B. inoculation in their cases.

Method

We have tried the drug in the clinical investigation ward of the King Edward Memorial Hospital in six cases—three males and three females, all being adults. Details of these cases are given in the Table. In all of them blood culture was positive, the Vi phage types of *Salmonella typhi* isolated being "A" in three cases, "E_1" in one case, and ? (untypable) in two cases. These six cases were encountered during a period extending from the latter half of May to July, 1949. Typhoid fever being endemic in Bombay, it was not possible to collect all the cases from the same outbreak. The cases came from widely scattered parts of the city and from different walks of life: two were peons, one a hotel worker, one a nurse, and two were performing domestic duties. None gave a history of contact. In all probability the source of infection was different in each case (also compare the phage types, see above). None of the cases had previously been inoculated with T.A.B. vaccine. Five cases were severely toxic before the treatment was started and one was moderately toxic. Two of the cases (Nos. 2 and 5) had received previous type-specific parenteral phage therapy without any demonstrable benefit.

All the six cases were observed in the investigation ward meant for treatment of typhoid cases alone. Hence all the patients received the same general nursing and dietetic treatment (Patel *et al.*, 1947), the administration of the drug being the only controlled variable.

Chloramphenicol was started in the second week in one case, in the third week in three cases, in the fourth week in one case, and in the fifth week in one case. In the last two cases the drug was tried during a clinical relapse. The dosage schedule was uniform in all cases: 1 g. initially followed by 1 g. one hour later and 0.25 g. two-hourly day and night until temperature was normal for 48 hours. Then 0.25 g. three-hourly for the next 48 hours, and finally 0.25 g. four-hourly till a total dosage of 18 g. was given. However, only one case (No. 2) could be given the full 18 g. The response was dramatic, the temperature touching normal in 36 hours and remaining normal.

Owing to short supply the other two cases that recovered (Nos. 5 and 6) received 12 g. and 16 g. respectively. Both of them responded very well, the temperature coming down to normal in 24 and 48 hours respectively, but the former case relapsed after an afebrile period of 12 days. This might probably indicate that 12 g. was an inadequate dose. During this relapse *Salm. typhi* were again isolated from the blood. As chloramphenicol was unobtainable the relapse could not be treated with it.

The other three patients died. They received chloramphenicol orally for 48, 26, and 40 hours respectively, the amount of drug given being 8, 5.5, and 6 g. respectively.

Case 1 received 8 g. of chloramphenicol in 48 hours. This patient should have at least started responding (cf. Bradley, 1949: in nine treated patients the signs of resolution were obvious within 48 hours—i.e., after the administration of 8 g. of the drug), but she rapidly developed peripheral vascular failure and died. Owing to her early death No. 3 apparently received inadequate dosage. In Case 4 the patient developed a rigor about 24 hours after starting the treatment. She went into hyperpyrexia and died 16 hours later.

Table Giving Various Data of Six Cases

Case No.	Age and Sex	Vi Phage Type	Previous Specific Treatment	Initial Toxicity	Day of Disease on which Treatment Started	Duration of Treatment	Total Dosage	Temperature Normal in Hours	Toxic Reactions	Result	Comment
1	25 F	A	Nil	Severe	28th	48 hours	8 g.	—	—	Died	Case of clinical relapse with bacteriaemia
2	23 M	?	Parenteral phage therapy	,,	35th	6½ days	18 g.	36	—	Cured	,, ,, ,,
3	38 M	?	Nil	,,	11th	26 hours	5·5 g.	—	—	Died	Probably chloramphenicol did not get a chance to act
4	24 F	E_1	Nil	,,	17th	40 ,,	6 g.	—	Rigor	,,	Patient went into hyperpyrexia and peripheral vascular failure
5	20 F	A	Parenteral type-specific phage therapy	Moderate	19th	70 ,,	12 g.	24	—	Cured	Dramatic response in a phage failure case. Relapse after an afebrile period of 12 days
6	25 M	A	Nil	Severe	15th	6½ days	16 g.	48	Erythemo-papular rash	,,	Rash disappeared in 3 days

Results

In all the three cases that recovered the temperature fell by crisis or rapid lysis in 24–48 hours. This is the usual experience of other workers in most of their cases. In all these three cases the constitutional improvement was

striking and was seen earlier (within the first 24 hours) than the fall in temperature. Woodward *et al.* (1948) had a similar experience. Shah (1949), however, finds just the reverse thing. In his opinion the effect on the toxic state is slower than the effect on fever. The fall in temperature occurs in two stages (Murgatroyd, 1949 ; Vakil, 1949). An initial fall is followed by a rise, the temperature then subsiding gradually. This was seen in two of our cases.

Toxic Reactions.—Chloramphenicol seems to be non-toxic for all practical purposes (Murgatroyd, 1949 ; Shah, 1949 ; Vakil, 1949). One of our cases developed a transitory erythemo-papular rash, mainly on the trunk. A similar finding has been noted by Shah in one case. The rigor that occurred 24 hours after the beginning of treatment in Case 4 may not have been a symptom of drug toxicity. It could well have been a hyperpyrexial reaction during the course of the disease, or it may have been due to rapid lysis of a large number of organisms. It is only tentatively included here, because it has not been observed by other workers. Shah found signs of cerebral irritation in seven cases. We did not come across any other toxic reactions, neither did Woodward *et al.* However, Shah and Vakil attribute nausea, anorexia, diarrhoea, circulatory failure, oliguria, and retention of urine in some cases to chloramphenicol. The cause of death in Case 1 in the present series was circulatory failure, but whether this was due to the drug or the disease it is difficult to say. Vakil describes a tendency to leucopenia.

Relapse.—One of our cases (No. 5) relapsed after chloramphenicol therapy and after an afebrile period of 12 days. The blood culture became positive during the relapse.

Vakil has noticed relapse following chloramphenicol therapy in two cases, and Shah found one relapse in his blood-culture-positive cases and four cases of relapse if his whole series of 33 cases is considered. In three of Shah's cases the relapse occurred during maintenance therapy and in one case after an afebrile period of nine days. Woodward *et al.* found that in the doses used chloramphenicol did not prevent relapses. He came across relapses with bacteriaemia in two cases after an afebrile period of 10 and 16 days. Both responded to a second course of the antibiotic. The organisms isolated during these recurrences were as sensitive to chloramphenicol as before. Shah's cases, too, responded to further chloramphenicol therapy.

Complications.—It has been shown by Woodward *et al.* that chloramphenicol does not prevent intestinal perforation and haemorrhage even in the afebrile period of the disease. After treatment with it one of his cases developed intestinal perforation on the second day of normal temperature, and another case had massive intestinal haemorrhage on the fourth day of normal temperature. Such complications were also encountered by Vakil. In our small series we have not come across these complications.

Duration of Fever After Institution of Chloramphenicol Therapy.—The average duration was 3.5 days with Woodward *et al.* and 1.5 days in our cases. The average duration of the afebrile course of the disease was approximately 12.5 days, whereas in Woodward's control group it was 35 days.

Urine Cultures.—The urine cultures before, during, and after chloramphenicol treatment have been found to be consistently negative by Woodward *et al.* The urine cultures were not done in the present series.

Stool Cultures.—Positive stool cultures after chloramphenicol therapy are well known (Woodward *et al.*, 1948 ; Murgatroyd, 1949 ; Rumball and Moore, 1949). Murgatroyd's case had a stool culture positive for *Salm. typhi* after the course of chloramphenicol. Woodward *et al.* found positive stool cultures in two cases ; later these became negative. Rumball and Moore treated a 9-year-old chronic faecal typhoid carrier with 30 mg. chloramphenicol per kg. of body weight (i.e., three times the therapeutic dose) for seven days, and the boy still continued to pass typhoid bacilli in the stools. This was surprising in view of the fact that *Salm. typhi* are inhibited *in vitro* by 0.25 μg. of chloramphenicol per ml., while in the usual therapeutic dose the blood level attained is 40–80 μg. per ml. (Woodward *et al.*, 1948).

Blood Culture.—With chloramphenicol therapy the blood cultures become sterile, but turn positive during a relapse. This is what we observed in Case 5.

Comment

Our series is too small for any statistical evaluation of the drug ; neither is the series ideal for such a purpose, because in none of the cases was the treatment started in the first week. We agree with Bradley (1949) that the advantages of chloramphenicol cannot be fully explained or exploited until the effect on cases in the first week of the disease is measured. It may be mentioned that Shah has tried chloramphenicol in six blood-culture-positive cases (out of his series of 17 cases). In four of these the treatment was started in the first week. All these cases have recovered dramatically and without any complications following on it. Chloramphenicol is more effective in typhoid fever than aureomycin, and that, too, in a smaller dose per kg. of body weight (Patel *et al.*, 1949). We believe that the drug is the most effective therapeutic agent available at present against typhoid fever.

Summary

Six culture-positive typhoid cases treated with chloramphenicol are reported.

It is plain that chloramphenicol strikingly alters the course of typhoid fever by exerting a specific therapeutic action. However, an extensive controlled trial is necessary to determine the optimal dose.

References

Bradley, W. H. (1949). *Lancet*, **1**, 869.
Ehrlich, J., Bartz, Q. R., Smith, R. M., and Joslyn, D. A. (1947). *Science*, **106**, 417.
Murgatroyd, F. (1949). *British Medical Journal*, **1**, 851.
Patel, J. C., Banker, D. D., and Modi, C. J. (1949). *Aureomycin in Typhoid Fever*. Report to the Therapeutic Trials Committee of Indian Research Fund Association (to be published).
—— Monteiro, L., Banker, D. D., and Kapadia, B. P. (1947). *Indian Physician*, **6**, 271.
Rumball, C. A., and Moore, L. G. (1949). *British Medical Journal*, **1**, 943.
Shah, M. J. (1949). *Indian Physician*, **8**, 192.
Vakil, R. J. (1949). Ibid., **8**, 185.
Woodward, T. E., Smadel, J. E., Ley, H. L., jun., Green, R., and Mankikar, D. S. (1948). *Ann. intern. Med.*, **29**, 131.

The Cerebral Palsy Unit at Queen Mary's Hospital for Children, Carshalton, Surrey, was opened in January, 1943, and was the first of its kind in Great Britain. There has since been set up an "advice clinic" at the Lambeth Hospital, where cases of cerebral palsy are assessed from the point of view of suitability for treatment and where parents and relatives are given advice about the management of cerebral palsied children. A booklet has now been produced presenting advice to parents and others on daily treatment, schooling, rest, speech, and other points. The booklet, which is well produced, contains a number of black-and-white sketches and gives useful information in the form of question and answer. Copies may be obtained from the hospital at Carshalton (price 1s.).

PNEUMOCOCCAL MENINGITIS OF REFRACTORY TYPE TREATED BY REPLACEMENT OF C.S.F. WITH PENICILLIN

BY

ALASTAIR ARNAUD REID, M.B., B.S.

Resident Medical Officer, Cornelia Hospital, Poole, Dorset

Does the pneumococcus develop resistance to penicillin? It would seem from a study of the following case that it does, although such resistance has not, so far as I know, hitherto been noted.

Case Report

The patient, a female child aged 13 months, was admitted to hospital as a typical case of bronchopneumonia, which responded in three days to a combined course of sulphamezathine and penicillin. She then appeared to be well for a fortnight, but at the end of this time the pneumonia recurred and did not respond to treatment.

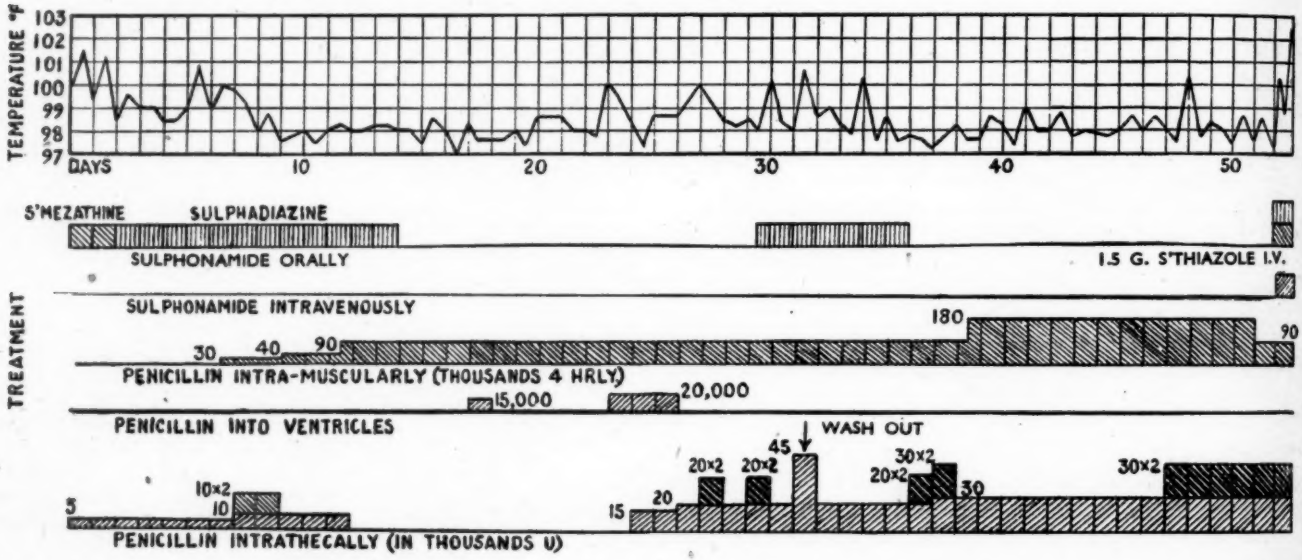
Twenty-four days after the beginning of the illness slight neck stiffness was noted and was thought to be due to meningism. Nevertheless, a lumbar puncture was performed and C.S.F. under normal pressure was withdrawn. Contamination with blood precluded its immediate examination, but a typical culture of encapsulated lanceolate diplococci was obtained, giving a diagnosis of pneumococcal meningitis. Later examination of the C.S.F. confirmed this. The organisms were tested against penicillin and were found to be moderately sensitive. (The test used was a modification of the filter-paper method which was in vogue at that time. On this occasion the strain was inhibited by a concentration of 5–10 units of penicillin per ml.) Lumbar puncture was immediately repeated, turbid fluid under increased pressure was withdrawn, and intrathecal penicillin therapy was begun, details of which are given in the Chart. (The days are numbered from the beginning of treatment for meningitis.) On the fifth day neck stiffness had almost disappeared and the C.S.F. was found to be nearly normal, as judged by the glucose level, which experience showed to be the most sensitive index to the state of the infection, and the first figure to be affected by either an increase or a decrease in its severity.

On the sixth and seventh days, however, relapse occurred in spite of treatment. Neck stiffness became pronounced and the fluid again became turbid. Sensitivity of the organism to penicillin *in vitro* was now found to be slight (growth inhibited by 10–20 units per ml.). Accordingly the dosage was increased, 10,000 units being given intrathecally twice daily. The results were dramatic, for in less than 72 hours the C.S.F. was quite clear. The sugar had returned to normal, but there was still some neck stiffness. Improvement continued until the 18th day, when the C.S.F. again became cloudy, with an increased cell count. It was decided that, as penicillin given by lumbar puncture was unlikely to inhibit organisms in the exudate at the base of the brain, the drug should also be given into the ventricles so that it could penetrate with the C.S.F. every part of the circulation. This was done, with some improvement.

It was felt, however, that it was possible that once the penicillin in the C.S.F. had been brought to a high level it could be maintained by heavy intramuscular doses. That this was probably correct is shown by the fact that improvement was maintained for some days by intramuscular dosage alone, until unfortunately, by a mischance, the intramuscular penicillin was stopped one evening. Next morning the meningitis had recurred in a severe form with tooth-grinding and neck stiffness. The C.S.F. was turbid and teeming with encapsulated pneumococci, which were now said to be completely resistant *in vitro* up to 25 units of penicillin per ml. (24th day).

However, as the Queckenstedt test was normal and as indigo carmine injected into the ventricle appeared at lumbar puncture next day, thus demonstrating patency of the system, it was decided to resume intensive treatment (24th day). This produced some improvement, but on the 28th day, in view of the sharp drop in the sugar, it was decided that the only hope lay in more drastic treatment.

Both clinically and *in vitro* the resistance of the organism had appeared to rise, necessitating repeated increase in the dosage of penicillin. As strong solutions of penicillin are irritant it was decided that the only practicable thing to do was to replace the infected C.S.F. with penicillin solution of a safe concentration. It was thus hoped to spread the penicillin as evenly as possible over the whole system.



Consequently, on the 32nd day simultaneous puncture of the right ventricle and the lumbar region was performed. Indigo carmine (3 ml.; 1%) was injected by the lumbar needle to serve as a marker, and it was followed by 45 ml. of penicillin solution (1,000 units per ml.). The dye appeared through the ventricular needle and both needles were then withdrawn. There were no ill effects from the operation and great improvement in the C.S.F., the sugar rising sharply in spite of the dilution by saline. The cells increased greatly (see Table), but as all were old and degenerate it was almost certainly due to the "stirring up of the mud" all the way up the cord and the base of the brain.

Table Showing Cell and Sugar Content of C.S.F.

Day	Cells per c.mm.	Sugar mg./100 ml.	Day	Cells per c.mm.	Sugar mg./100 ml.
2	1,700	39	33	2,200	75
5	610	66	35	160	78
6	280	31	37	130	70
7	1,800	33	39	280	51
9	360	92	43	65	66
12	28	65	44	290	59
18	800	59	46	140	47
24	—	25	47	20	61
27	4,000	54	50	14,560	57
28	1,000	29	52	210	65
31	100	63	53	20,000	17

Paracolon bacilli were found on days 50, 51, 52, and 53.

During the next few days the patient improved, but intensive penicillin therapy was continued in order to keep up the concentration in the C.S.F. By the 37th day the cerebral cry had quite disappeared, as had the neck stiffness. During the succeeding days, although the condition of the meningitis fluctuated, the child improved greatly. She began to resist treatment forcibly, to eat well, and to play with her toys. Up to the 47th day honours were divided between the penicillin and the organisms, although the Queckenstedt test remained normal. Repeated examination of the nose and ear by an E.N.T. surgeon again revealed no source of reinfection.

On the 53rd day, however, there was a disastrous relapse. The neck became retracted and the C.S.F. purulent and under increased pressure. Paracolon bacilli (first noted in a culture four days before) were seen in large numbers in a smear, although no pneumococci were present. In spite of double cleaning with iodine, these bacilli had presumably been introduced from the skin by the needle. The "cerebral cry" returned, and in spite of intensive intravenous sulphonamides the patient became collapsed and comatose. Convulsions developed at 8 p.m. and death came three and a half hours later. Unfortunately it was impossible to perform a post-mortem examination, invaluable as this would have been.

Discussion

The infecting organism rapidly developed an apparent resistance to penicillin *in vitro* (at least according to the tests used at that time), but it was still possible to kill it *in vivo* by means of large doses. It appeared likely that the case would ultimately have become chronic in the same way as do some cases of tuberculous meningitis treated with streptomycin, relapse occurring as soon as the drug is withdrawn. Because large doses of intrathecal penicillin were known to be dangerous, this case was at first treated too conservatively. The initial doses should have been bigger and given twice daily. If this had been done the organism might have been destroyed before it became resistant. In a case of meningitis of this severity large doses are worth the risk. The child seemed to suffer no ill effects from the use of huge intrathecal doses. It seems that it is local concentration, not dosage, which is dangerous, but it is dosage or general concentration which is important therapeutically. C.S.F. lavage and replacement with penicillin offer a reasonable method of achieving this general concentration safely, and a technique has been developed and found to be satisfactory. C.S.F. replacement had no ill effects. It is also possible, while doing this, to demonstrate with dye the patency of the foramina of Magendie and Luschka. This is important in prognosis.

Finally, it is known that penicillin is poorly excreted into the C.S.F., but it has been demonstrated clinically that large intramuscular doses can keep up the concentration once this has been achieved by intrathecal administration.

The case demonstrates the necessity for a bold approach and decision in the treatment of pneumococcal meningitis. Intensive treatment, with close observation and frequent laboratory examinations, is essential if the disease is not to become chronic, and if a final cure is to be achieved.

Summary

A case of pneumococcal meningitis is described in detail. Apparent growth of resistance to penicillin on the part of the organisms is demonstrated, and the necessity for maintaining a high concentration of the drug in the C.S.F. is shown. C.S.F. replacement therapy and its results are described, and it is shown that penicillin concentration in the C.S.F. can be maintained by intramuscular dosage. A technique for demonstrating patency of the foramina in the roof of the fourth ventricle is given.

Acknowledgments are due to Dr. C. Adamson, of Durham County Hospital, for permission to publish the case, and to Mr. P. O. D. Hopps for his invaluable work in the laboratory.

Medical Memoranda

Chloramphenicol in Typhoid Fever

In view of preliminary reports of cases of typhoid fever treated by chloramphenicol (chloromycetin) (Bradley, 1949; Murgatroyd, 1949), it is considered that publication of the following case may be of interest.

Case Report

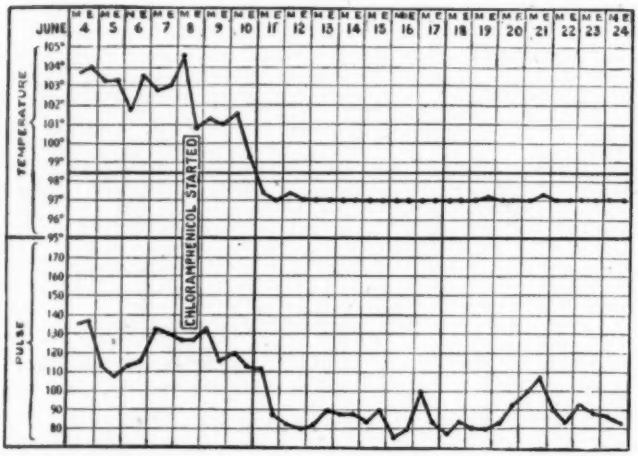
A Service patient aged 20 was admitted to hospital on June 4, 1949, with a provisional diagnosis of typhoid fever. Preventive inoculation with T.A.B. was reported to have been given in February, 1949.

He had sailed from Port Said on May 21 and first felt unwell on May 26, complaining of headache, vomiting, and sore throat. He disembarked at Southampton on May 31 and travelled by train to his home in Nottinghamshire. He still complained of frontal headache, had several rigors, and also complained of marked generalized weakness. On June 2 he had epistaxis, and on the following day was admitted to the medical ward of a general hospital for P.U.O. A few papules were noticed on the abdomen on June 4, and he was transferred to an isolation hospital. There was no history of constipation or diarrhoea.

On admission his temperature was 104° F. (40° C.), pulse 138, and respirations 26. He was mentally confused, answered questions slowly, and had difficulty in pronouncing words. There were a dozen rose-coloured spots on the front of his abdomen, which was distended but resonant. The spleen was not palpable. There were no other physical signs except a coarse bilateral nystagmus which was congenital. His condition deteriorated until on June 6 he was comatose and could not be roused. The eyes were sunken, the tongue was covered with a brown fur, and there was muttering delirium with purposeless picking at the bedclothes. The rash was heavy on the chest and buttocks, and there was retention of urine. Constipation was marked, and it continued throughout the illness. The white cell count was 6,000 (polymorphs 78%, lymphocytes 19%, eosinophils 2%, and monocytes 1%). No abnormal red or white cells were found, and films showed no malaria parasites. The urine was sterile, but a non-lactose-fermenter was grown on blood culture.

On June 8 the pulse was irregular and he showed signs of hypostatic pneumonia. At this stage a supply of chloramphenicol was obtained and an initial dose of 16 capsules (4 g.) was given by nasal tube. This was followed by six capsules (1.5 g.) with glucose twice daily for four days. Two days after treatment was started there was such a remarkable improvement in his condition that he was able to swallow capsules and fluids normally and to answer questions, although his speech was slurred and indistinct. On the following day (June 12) temperature, pulse, and respirations had returned to normal (see Chart) and he asked for food and permission to

walk round his bed. Chloramphenicol was continued with a dosage of three capsules twice daily for a further week, making a total dosage of 33½ g. He made an uninterrupted recovery except for slight hoarseness of voice lasting two days, and when seen in August he was feeling very well and had regained his usual weight.



Bacteriological Results.—June 4:—Supplementary report from Salmonella Reference Laboratory: Blood culture organism has the following antigenic structure: O = IX, XII (Vi); H=d. Therefore it is *Salmonella typhi.* Dr. Felix, Central Enteric Laboratory, reported that the culture belonged to an untypable Vi strain (dégraded). June 8: Faeces positive for *Salmonella typhi.* The patient's serum gave a positive agglutination with this organism to a titre of 1/250. June 14:—Blood Widal test: *Typhosus*, H −, O 1/250; *paratyphosus A*, H −, O 1/500; *paratyphosus B*, H −, O 1/250.

Three subsequent specimens of faeces and urine showed no pathogens, and he was discharged from hospital in excellent health on July 7. A subsequent examination of faeces on August 11 was negative for organisms of the enteric group.

W. LOMAX, M.D., D.P.H.,
Isolation Hospital, Doncaster.

REFERENCES

Bradley, W. H. (1949). *Lancet*, **1**, 869.
Murgatroyd, F. (1949). *British Medical Journal*, **1**, 851.

Staphylococcal Portal Pyaemia

This condition has a grave prognosis, and before the introduction of penicillin was nearly always fatal. In the following case a severe infection of several weeks' duration was cured by combined penicillin and sulphonamide therapy.

CASE REPORT

The patient, a fitter aged 31, was referred to hospital with a diagnosis of infective hepatitis. His illness had apparently commenced three weeks previously with complete loss of appetite followed by severe upper abdominal pain, constipation, and vomiting. A few days before admission he noticed his urine was dark and his faeces pale. Before this illness the patient had been troubled with recurring carbuncles of the skin, but had not received any chemotherapy. The last one occurred on the buttock and had healed two weeks before his present symptoms began. He had served in the Middle East during the war and gave a history of several attacks of malaria, but none of dysentery.

On examination he was pale and thin. Icterus was observed in the conjunctivae but not in the skin. The temperature was 100.4° F. (38° C.). There was epigastric tenderness, but no enlargement of the liver or spleen, and no ascites. The urine showed a trace of bile.

The patient's temperature rose the following day to 102° F. (38.9° C.), and thereafter exhibited a daily swing from 99 to 103° F. (37.2–39.4° C.). Blood count showed: haemoglobin 83%; white cells 31,800 per c.mm. (polymorphs 91%, lymphocytes 7%, monocytes 2%). The clinical picture was unlike that of infective hepatitis, which view was supported by the results of liver function tests (thymol turbidity, 1 unit; thymol flocculation, 0; alkaline phosphatase (Jenner and Kay) 19.2 units). His condition deteriorated rapidly. The jaundice became deeper, and was apparent in the skin as well as the conjunctivae; the liver became tender and enlarged to four fingerbreadths below the right costal margin. The abdominal pain was almost constant and became very severe. The haemoglobin fell to 66% and the white cells increased to 41,000 per c.mm. The patient was now dehydrated, thin, and desperately ill. He vomited on several occasions and had severe anorexia.

One week after admission he complained of pain in both shoulders, and these joints became swollen, hot, and painful to move. The diagnosis of pyaemia with multiple liver abscesses and suppurative arthritis of the shoulder joints then became apparent, and was confirmed by a blood culture. The organism was a penicillin-sensitive *Staphylococcus aureus.* A few days previously a needle biopsy of the liver (performed by Dr. H. A. Dewar) showed infiltration of the portal tracts with polymorphs. A fluoroscopic examination did not show any elevation or restricted movement of the diaphragm.

Penicillin, one million units daily, was started on the tenth day after admission. After three days the evening temperature was still 102° F. (38.9° C.). The next day sulphamezathine was added; the temperature fell rapidly to normal and the patient's condition improved dramatically. His appetite returned, the jaundice faded, and the liver diminished in size and lost its tenderness. He began to put on weight and became lively and cheerful. The penicillin was continued for ten days and the sulphamezathine to a total dosage of 40 g. The swelling and pain in the left shoulder joint subsided, but the right shoulder remained painful and stiff. There was no radiographic bone or joint change. The affected joint was treated by immobilization in a sling for three weeks, followed by exercises and heat. During this time the patient showed a steady improvement and the temperature did not rise above normal. He was discharged after a month in hospital.

Six weeks later he was feeling well and was free of symptoms, apart from some residual stiffness in the right shoulder.

COMMENT

The diagnosis of pyaemic abscesses of the liver was assisted in this case by the development of metastatic arthritis in the shoulder joints. Both lesions were complications of a systemic pyaemia which appeared to follow a carbuncle. The suddenness of the hepatic enlargement was a striking feature, and was similar to that observed by Wyndham (1945) in each of his three cases. The appearance of jaundice may be taken as an indication of the severity of the infection, for it is regarded by several authors (Rothenberg and Linder, 1934; Ochsner *et al.*, 1938; Smith, 1944) as a late and infrequent sign of ominous significance occurring only when the abscesses are multiple and widespread throughout the organ.

I wish to express my thanks to Dr. A. G. Ogilvie for permission to record this case.

CHRISTOPHER STRANG, M.B., M.R.C.P.,
Royal Victoria Infirmary, Newcastle-upon-Tyne.

REFERENCES

Ochsner, A., DeBakey, M., and Murray, S. (1938). *Amer. J. Surg.*, **40**, 292.
Rothenberg, R. E., and Linder, W. (1934). *Surg. Gynec. Obstet.*, **59**, 31.
Smith, R. S. (1944). *Amer. J. Surg.*, **63**, 206.
Wyndham, N. (1945). *Med. J. Aust.*, **1**, 252.

Reviews

PRACTICE OF OPHTHALMOLOGY

Modern Practice in Ophthalmology, 1949. Edited by H. B. Stallard, M.B.E., F.R.C.S. (Pp. 525; 231 illustrations; 30 coloured plates; £3 5s.) London: Butterworth. 1949.

The Modern Practice series is written for the general medical practitioner as a guide when he shares with a consultant the responsibility of the conduct of a case ordinarily outside his province, or when it falls to his lot to act on his own responsibility when the consultant is not available. The present volume on ophthalmology is written by 14 well-known contributors under the general editorship of Mr. H. B. Stallard, who has written several sections himself.

A book of this type is difficult to prepare. Obviously it cannot be comprehensive, and there are few decisions requiring more judgment than the selection of the essentials and the discarding of the non-essentials. Ophthalmology presents more problems in this respect than any other branch of medicine, for it is peculiarly specialized and the effects of disease of the eye may be dramatic and catastrophic. The tendency for most books of this type is to be encyclopaedic, treating the diseases of each tissue systematically. This is the style of the present volume, and without question each section is good and its teaching reliable.

As a rule, however, disease presents itself to the general practitioner in a different way. In his experience the essential problem is to assess the importance of such questions as the significance of a red or a painful eye. The answer would be difficult to find from the present book unless the reader consulted a multitude of headings and studied the differential diagnosis of each. To take another example, a common complaint addressed to the general practitioner is that of double vision. Reference to the index leads to a description of diplopia goggles in testing for squint. There is, however, an excellent section on ocular palsies in the chapter on medical ophthalmology, a separate section on paralytic squint written from the standpoint of muscular function, while in the chapter dealing with cataract uniocular diplopia (the commonest cause of double vision in practice) is noted. This tendency is accentuated, to take a further example, in the duplication of the discussion of the vascular retinopathies and of vascular occlusions. These lesions are extensively described in the chapter on medical ophthalmology, and the discussion is repeated by a different author in another chapter dealing with diseases of the retina. Both sections are well illustrated, but there is no cross-reference to the text or the illustrations. The best chapter, from this viewpoint, is that on the cornea. The subject is treated non-compartmentally, and an account is given of the different types of corneal lesion, their main causes, the main symptoms and signs of corneal disease, the main features providing aetiological clues, what conditions elsewhere may throw light on the local lesion, the prognosis, and the general principles of treatment. The presentation of the subject-matter in this case makes it relatively easy for the practitioner (who is always assumed to have forgotten his ophthalmology) to use the book as a useful vade-mecum.

The book is well produced, and the illustrations are lavish and excellent. As is to be expected in a work of this type, most of these are not original but are derived from periodicals or other books: for the use of these the publishers have been acknowledged but not the authors—an omission which, it is hoped, will not become a practice in British medical literature.

STEWART DUKE-ELDER.

TEXTBOOK OF HAEMATOLOGY

Hematology. By Cyrus C. Sturgis, M.D. (Pp. 915; illustrated. £3 3s.) Oxford: Blackwell Scientific Publications. 1949.

An author intending to write a new general textbook of haematology must face the fact that there is already one superlatively good work on the subject—Wintrobe's *Clinical Hematology,* published in 1942. Yet it is evident that no textbook, however good, can dominate the field indefinitely. Time by itself favours the new work, because research on haematology is active and every year there is much to add and a little to take away. Moreover, many different approaches are possible, and a new publication may be welcome simply because it is written from a new viewpoint.

The strongest feature in the present book is its historical approach, and for this alone it will be a valuable work of reference. For instance, anyone trying to understand why forty years ago anaemic adolescent girls turned green, whereas now they simply turn pale, will be comforted to read Cabot's description, written in 1915: "It takes the eye of faith to see any justification for the title of the disease [chlorosis]. . . . If one exercises a great deal of imagination, one might possibly see the slightest imaginable tint of olive green in the shadow beneath the chin, that is all."

Perhaps the chief weakness of the book is its lack of interest in methods and standards; indeed, methods are not described at all, and in the first paragraph the author is content to refer to values obtained in a group of persons "in the vicinity of Ann Arbor." Nowhere is mentioned the problem of obtaining consistency between different centres in making haemoglobin estimations, or of the innumerable sources of error in haematological methods.

A book published in 1948 ought not to have to admit that "the separation of acquired . . . hemolytic anemia with acholuric jaundice [from the congenital form] . . . causes considerable difficulty." This statement ignores the fact that two methods of distinguishing between these conditions are now known: first, erythrocyte survival tests, and, secondly, the direct Coombs test. Further examples of the rather patchy treatment of recent work are as follows: no mention of the work on the anaemia of infection by Wintrobe and his co-workers; no reference to the iron-binding protein or to the Rh "blocking" antibody; no mention of the use of urethane in the treatment of leukaemia or of the advantage of adding citric acid to citrate-glucose mixtures for blood preservation.

In short, this book cannot be regarded as a first-class scientific work, but it can be strongly recommended as a very readable introduction to haematology which should prove useful to anyone who wishes to know more of the history of any particular syndrome.

P. L. MOLLISON.

THE TECHNIQUE OF TRANSFUSION

Blood Transfusion. By Elmer L. De Gowin, M.D., Robert C. Hardin, M.D., and John B. Alsever, M.D. (Pp. 587; 200 diagrams. £2 5s.) Philadelphia and London: W. B. Saunders Company. 1949.

The three authors of this book were all concerned with the organization and running of blood banks in the United States during the recent world war, and one of them was responsible for teaching the facts of blood transfusion in

the Army. During these activities they all came to feel the need for a book covering the entire field of blood transfusion, and the present volume is designed to cover this deficiency. The volume is large and certainly contains a great amount of information about transfusion, but it does not form a really comprehensive treatise on the subject. The emphasis throughout the volume is on the technical side, and the result is an admirable practical handbook. Its chief value will be for the laboratory worker and those employed in blood banks; the clinician will not find in it a readable account of the medical and surgical sides of the subject. An important feature of the book is what the authors call "a series of flow diagrams." These are marginal line drawings illustrating the steps of the various technical processes, so that the operator may acquire his technique with the least effort of the mind. The diagrams have been admirably done by the instructor in art at the State University of Iowa.

In their preface the authors deplore the fact that blood transfusion has become a minor specialty, but they believe that the necessity for this is genuine. A blood transfusion cannot be carried out simply as it used to be, though the process can be done largely by technicians. The present volume certainly produces the impression that the physicians and surgeons can now take back seats in the transfusion arena, and that the philosophy of blood transfusion is a matter of little importance.

GEOFFREY KEYNES.

RADIOLOGIST AND CLINICIAN

Confrontations: Radio-Anatomo-Cliniques. By De M. Chiray, R. A. Gutmann, and J. Sénèque. (Pp. 79; 150 figures. 1,000 francs.) Paris: G. Doin, Masson. 1949.

In this symposium from a number of Paris hospitals some forty case histories are presented in such a way as to bring together the *x*-ray appearances, the pathological anatomy, and the clinical course. About half of each page is taken up with illustrations, and the *x*-ray reproductions and pathological photographs are excellent. The quality of the case histories varies, but in most of them the reader feels he is given an insight into the way the clinician's mind worked when they were taken. Many phrases have that epigrammatic clarity which is typical of French medicine at its best, and which is so difficult to imitate in other languages. Considerable space is allotted to highly critical commentaries on the *x* rays.

As might be expected from the editors' interests, the problems are mainly gastro-enterological. However good the radiological and gastroscopical technique, it is often impossible to decide whether a distortion of the pyloric antrum is due to gastritis or carcinoma, whether a jejunal ulcer is present or not, and whether an ulcer is carcinomatous. In elderly subjects decisions on correct procedure may be fraught with anxiety, and in most clinics unnecessary mistakes probably occur in the borderland between clinical and *x*-ray responsibility. The moral of these studies is that the radiologist who takes a superficial clinical history and allows it to influence his diagnosis is a menace. Certain *x*-ray appearances make operation desirable, regardless of the diagnosis suggested by classical clinical medicine. On the other hand, the clinician cannot shift his responsibility on to the radiologist. It is his duty repeatedly to ask himself whether all the symptoms can be explained by the *x*-ray findings or whether an alternative explanation is essential. The *x*-ray department can only be as good as the clinicians allow it to be, and without the fullest collaboration mistakes and mutual recriminations are inevitable.

The value of the book lies in the cases it describes. They are too uncommon to be properly dealt with in a textbook, and too common to find a place in ephemeral journals. In addition, few textbooks or journals could afford the lavish but essential illustrations.

D. A. JENNINGS.

HYPNOSIS

Medical Hypnosis. By Lewis R. Wolberg, M.D. (Volume 1: pp. 449; $5.50. Volume 2: pp. 513; $6.50.) New York: Grune and Stratton. 1948.

These handsomely produced volumes provide an account of theory and practice in hypnosis which has been largely oriented by psycho-analytic teaching. Thus, in his interesting chapter on the nature of hypnosis the author rejects one by one theories of a neuro-physiological kind; and though he finds points of criticism in the usual psycho-analytic theory of hypnosis he finally adopts a theory which is little removed from it. Those who are not analysts will be inclined to criticize this critique. The psycho-analytic theory places great importance on the personal relationship between the hypnotist and the subject; the hypnotist becomes the "intrapsychic representative of the parent or superego." This would seem to be altogether too narrow a conception. The phenomena of hypnosis will be unintelligible until they are brought into relation with a very wide class of observations on both human and animal behaviour. The hypnosis of animals has been a frequent subject of experiment, and certainly cannot be accounted for by explanations involving the fabulous superego. Any satisfactory theory would have to be applicable to the phenomena of psychic shock, hysterical conversion symptoms, normal dissociative processes such as are seen in sleep-walking, the "miracle" cures of religious conversion, and many others, besides hypnosis itself.

In the author's view the applications of hypnosis in treatment are wide and varied, but they should always be a part of a consistent scheme of psychotherapy. He discusses the use of hypnosis for the simple removal of a symptom, as a part of non-analytic types of psychotherapy, reassurance, and persuasion, and as a technique to aid progress in psycho-analysis. Nearly every chapter of the second volume is profusely illustrated with recorded conversations between doctor and patient which effectively display the author's methods. In a final note the use of hypnosis for public displays is deplored, and the author demands protective laws which would confine the use of hypnosis to the medical profession.

ELIOT SLATER.

ADVANCES IN TUBERCULOSIS

Fortschritte der Tuberkulose-Forschung und -Behandlung. Edited by H. Birkhaeuser. Vols. 1 and 2. (Pp. 446. 45.40 Swiss francs.) New York and Basle: S. Karger. 1948.

In this account of progress in research and treatment in tuberculosis abstracts have been compiled of those items of wartime literature which "seemed to the authors, on the basis of their special knowledge, worthy of notice." There are 19 articles, unequal in value and scope, and on entirely different aspects of tuberculosis. Most of them are without comment or criticism.

The best of these articles are: H. Bloch's account of the morphology, chemical constitution, and pathogenicity of the tubercle bacillus; "Experimental Pathology and Therapy," by Noel Rist; "Collapse Therapy," by Haeberlin; and "Sarcoidosis," by Loeffler and Jaccard. The workers on sarcoidosis concluded that the condition

was marked by well-defined clinical and histological characteristics. In their opinion this did not exclude a tuberculous aetiology, nor did it favour it. That sarcoidosis can be followed by tuberculosis may be due to a special predisposition. Uehlinger's case, in which sarcoidosis was followed by fulminant tuberculous septicaemia, may support this, but in the reviewer's opinion it was a single, exceptional case. As a rule, when sarcoidosis is followed by tuberculosis the latter is ordinary in appearance and course and lesions of both conditions can be found in intimate association with each other. The authors reject the virus hypothesis. From their suggestion that sarcoidosis should be catalogued as a disease of the reticulo-endothelial system they seem to expect some compensation for our ignorance of its aetiology.

W. PAGEL.

MORGAGNI'S SYNDROME

Morgagni's Syndrome. By Professor F. Henschen, M.D. (Pp. 172; illustrated. £1 10s.) Edinburgh and London: Oliver and Boyd. 1949.

The triad of hyperostosis frontalis interna, virilism, and obesity was first described by Morgagni in 1761, and in 1936 Professor Henschen suggested the term "Morgagni's syndrome." The hyperostosis which he considers the essential component of the syndrome is found in over half the population past 70, and is a necropsy finding rather than a clinical entity, for it is often symptomless. The syndrome itself is admitted by the author to be "a not very strongly pathologically accentuated variant of the endocrine state of the woman after the climacteric." People vary widely in their endocrine equipment, and there is some doubt whether Morgagni's syndrome has yet deserved to be christened. Syndromes are born easily but die with difficulty, and the bestowal of an eponym for some reason guarantees their longevity. Until doctors are clearer in their minds about what constitutes an abnormality, and until they decide how closely abnormalities must be associated to justify their being grouped together as a syndrome, there will always be doubts about the usefulness of a label. This book says, in effect, that many elderly, fat, hairy ladies have thick fronts to their skulls and nobody really knows why.

The volume is well produced and illustrated, and the thoroughness with which this painstaking work has been done results in a complete and authoritative survey of a very specialized subject.

RICHARD ASHER.

The purpose of the series of reviews of which *The Annual Review of Microbiology* (Editor, C. E. Clifton; pp. 532; £1 16s.; London: H. K. Lewis and Co.; 1948) is the second volume is not to survey the whole field of microbiology but to select about a score of important subjects in which significant advances have been made. Each topic is the responsibility of an expert contributor, who gives a critical summary of recent research. Much of this research is of a fundamental character, and it is assumed that the reader is familiar with earlier work. These reviews are thus designed primarily for those engaged in teaching and scientific research. The present volume contains articles on bacterial and protozoal metabolism and growth factors, on antibiotics and chemotherapeutic agents, and on chemical disinfectants. Immunology is represented by reviews on the nature of antibodies and complement and the inheritance of immunity, and systematic microbiology by papers on the pathogenic streptococci, spirochaetes, and the neurotropic viruses. There are also several articles on fungi, soil, and water which are likely to be of interest to industrial and agricultural bacteriologists. The contributors have succeeded admirably in producing a concise and readable summary of the work of the last few years, without notable omissions. The extensive lists of references are particularly valuable. The book will be welcomed by teachers and others whose duty it is to keep pace with the ever-increasing volume of new knowledge in microbiology.

BOOKS RECEIVED

[Review is not precluded by notice here of books recently received]

Homöopathie und Harmonische Ordnung der Heilkunde. By A. Bier. (Pp. 268. M. 19.50.) Stuttgart: Marquardt. 1949.

The Story of the Johns Hopkins. By B. M Bernheim, M.D. (Pp. 274. 12s. 6d.) Kingswood, Surrey: The Worlds Work (1913). 1949.

Science and International Relations. By J. Needham, F.R.S. (Pp. 30. 2s. 6d.) Oxford: Blackwell Scientific Publications. 1949.

Body and Mature Behaviour. By M. Feldenkrais. (Pp. 167. 12s. 6d.) London: Routledge and Kegan Paul. 1949.

Het Rubella-Probleem in het Licht van Nederlandse Ervaringen. By A. E. H. M. Kamerbeek. Foreword by J. P. Bijl. Vol. 14. (Pp. 212. 15s.) London: H. K. Lewis. 1949.

Autobiography of Dr. Robert Meyer. With a memoir by E. Novak, M.D. (Pp. 126. $2.50.) New York: Henry Schuman. 1949.

Neurocirugia. (Pp. 316. No price.) Santiago, Chile: Instituto Central de Neurocirugia y Neuropatologia. 1948.

Textbook of Bacteriology. By C. H. Browning, M.D., F.R.S., and T. J. Mackie, C.B.E., M.D. 11th ed. of Muir and Ritchie's *Manual.* (Pp. 907. 50s.) London: Geoffrey Cumberlege. 1949.

Dental Caries. By T. Ockerse, D.M.D., D.D.S. (Pp. 80. No price.) Pretoria: Department of Health. 1949.

The Energetics of Human Behavior. By G. L. Freeman, Ph.D. (Pp. 344. 20s.) New York: Cornell University Press. London: Geoffrey Cumberlege. 1948.

The Family in a Democratic Society. Anniversary Papers of the Community Service Society of New York. (Pp. 287. 21s.) New York: Columbia University Press. London: Geoffrey Cumberlege. 1949.

Hematology. By W. M. Fowler, M.D. 2nd ed. (Pp. 535. 44s.) London: Hamish Hamilton Medical Books. 1949.

Brain and Behaviour. By N. E. Ischlondsky, M.D. (Pp. 182. 21s.) London: Henry Kimpton. 1949.

Biochemistry in Relation to Medicine. By C. W. Carter, B.M., B.Ch., and R. H. S. Thompson, B.Sc., D.M. (Pp. 442. 25s.) London, New York, Toronto: Longmans, Green. 1949.

Ophthalmic Medicine. By J. Hamilton Doggart, F.R.C.S. (Pp. 329. 32s.) London: Churchill. 1949.

Tom Cullen of Baltimore. By J. Robinson. (Pp. 435. 21s.) London, Toronto, New York: Geoffrey Cumberlege, Oxford University Press. 1949.

Therapeutic Group Work with Children. By G. Konopka. (Pp. 134. 14s.) London: Geoffrey Cumberlege, Oxford University Press. 1949.

Rehabilitation of the Handicapped. Edited by W. H. Soden. Foreword by S. Licht, M.D. (Pp. 399. $5.) New York: The Ronald Press. 1949.

A Calendar of Food and Wine. By Nell Heaton and André Simon. (Pp. 268. 16s.) London: Faber and Faber. 1949.

Pharmacology and Toxicology of Uranium Compounds. Edited by C. Voegtlin, Ph.D., and H. C. Hodge, Ph.D. (Pp. 1,084. 60s.) London: McGraw-Hill. 1949.

Human Personality and its Minor Disorders. By W. Harrowes, M.D., F.R.S.Ed. (Pp. 260. 15s.) Edinburgh: E. and S. Livingstone. 1949.

The Anatomy of the Female Pelvis. By F. A. Maguire, F.R.C.S., F.R.C.O.G. 4th ed. (Pp. 176. 42s.) London: Angus and Robertson. 1949.

Trends in Medical Education. Edited by M Ashford, M.D (Pp. 320. 16s.) London: Geoffrey Cumberlege. 1949.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY OCTOBER 22 1949

FRESH LIGHT ON MALARIA

So much has been added to knowledge about the parasitology and treatment of malaria during the last decade that a total revolution of ideas has taken place. The new facts, however, have come in such a fragmentary manner, major and minor discoveries jostling each other, that at times they have seemed rather to complicate than clarify existing problems. In his Croonian Lectures—published in this and last week's *Journal*—Professor N. Hamilton Fairley has fitted the new pieces of knowledge together and enabled them to be seen in perspective. It seems that *Plasmodium vivax* and *P. malariae* exist in man in five distinct forms—the sporozoite, the pre-erythrocytic form in the liver, the schizont in the red blood corpuscle, the exo-erythrocytic form in the liver, and the gametocytes in the red cells. *P. falciparum* apparently does not develop the exo-erythrocytic form, but is otherwise similar. The sporozoite is merely a transitional stage inoculated by the mosquito, and it quickly changes into the pre-erythrocytic form, which then multiplies in the body. The schizont, which incidentally produces the fever, seems to be a rather unnecessary phase in the protozoon's life history, except that gametocytes perhaps branch off from it to constitute the form infective to mosquitoes. The exo-erythrocytic stage is not essential for the protozoon's survival, but provides a long-living resistant reservoir from which new broods of schizonts arise; these cause clinical relapses and are the source, directly or indirectly, of fresh gametocytes which may ensure the organism's ultimate survival.

Each of these forms reacts differently to drugs, and it is now hardly surprising that the old quest to find a drug which would eliminate the schizont and the fever it caused had little success in so far as the radical extermination of the parasite was concerned. Perhaps all forms are susceptible in some degree to the action of the known antimalarial drugs. Within the limits of tolerated doses quinine, mepacrine, and chloroquine are effective against schizonts only. In consequence they offer no prospect of radical cure of *P. vivax* infections, which may continue in the exo-erythrocytic form untouched by the drug. They are not true causal prophylactics, though when properly administered mepacrine and chloroquine may destroy the schizont so rapidly that clinical signs are suppressed; in consequence they appear to act as true prophylactics against *P. falciparum* infections and are good suppressants of the others. Proguanil has a wider range, acting on the pre-erythrocytic form of *P. falciparum* malaria as well as on the schizonts and gametocytes of all species. It is therefore a true causal prophylactic of *P. falciparum* malaria and a suppressant of *P. vivax* infections; it brings about a clinical but not a radical cure of *P. vivax* infections, and renders gametocytes non-infective to mosquitoes. The range of the 8-amino-quinolines — pamaquin, pentaquine, and iso-pentaquine—is still wider, for they have an observable effect on the pre-erythrocytic, schizogony, exo-erythrocytic, and gametocyte stages. This group is therefore the only one from which there is a prospect of obtaining an efficient antimalarial drug for the clinical cure, radical cure, and prophylaxis of all forms of malaria. Unfortunately the toxicity of these drugs makes them useless for the control of schizogony and its clinical effects or for prophylaxis, and for other purposes they should be administered under strict medical control. Efforts in the U.S.A. to discover less toxic members of this group have met with some success, for recent reports indicate that iso-pentaquine has a maximum tolerated dose about four times that of the original pamaquin, while weight for weight it is apparently slightly more effective. It is, however, still too toxic to be of any use as a prophylactic or schizonticide, or to be taken except under medical supervision. For the time being, then, until some drug is discovered with the range of action of the 8-amino-quinolines but without their toxicity, a variety of drugs must be prescribed, according to the purpose of medication and the species of parasite concerned.

Professor Fairley's account of the life history of the parasite is satisfying in that it explains all the known facts, and most of it has been objectively proved, but a great field lies open for further work. The pre-erythrocytic cycle of *P. falciparum* malaria is still hypothetical; happenings in the "premune" state are obscure; the relationship between "premunity" and reaction to treatment requires further investigation; there is no effective prophylactic against *P. vivax* malaria; the risk of parasites acquiring tolerance to proguanil and perhaps other drugs cannot be ignored; some of the available drugs are too toxic for common use; and the variety of drugs needed for the treatment of one disease is greater than desirable. In the past work has been slow because it has largely depended on human volunteers, often intentionally inoculated, in whom the course of events had to be laboriously studied for several months. The recent use of parasites of birds and monkeys has greatly eased the preliminary work, but this is not entirely satisfactory, because the relationship

[1] *British Medical Journal*, 1949, **2**, 222.

between avian and human parasites is insufficiently close, and the monkey is an expensive and difficult animal for large experiments. More rapid progress could be made if the human parasites could be cultured in ordinary laboratory animals or if a closely related parasite could be found in one of them. The discovery of a new *Plasmodium* (*P. berghei*) in Congo tree rats holds out hope that the second of these conditions may be fulfilled. It is not yet certain that it will be, because mosquito transmission, not mere blood inoculation, must be maintained, and the anopheline vector, probably *Anopheles dureni*, has not been finally confirmed or established by culture in Europe or America. If the difficulties in using this parasite could be overcome and large stocks of the rats infected by mosquito transmission maintained, it should be possible to screen drugs in a much more realistic manner than before by tracing their immediate effects on each form of parasite by post-mortem examination. Chemotherapeutic research would thus be greatly accelerated, though the need for final confirmation on man would remain.

These advances in the treatment of malaria come at a time when its prevention is being undertaken on a rapidly increasing scale. Total extinction, eliminating the need for treatment, is still beyond the vision of even the most enthusiastic. Progress in mosquito control—a subject discussed in a recent leading article[1]—has, however, advanced to the stage when many doubt the place of mass therapy or drug prophylaxis in the protection of the civilian population except during epidemics, believing that the funds and administration needed for them could more effectively be used in mosquito control. The field of treatment is, therefore, becoming narrower in comparison with past years, but this is all to the good if it means that blunderbuss therapy gives way to the practice of scientific medicine.

TUBERCULOSIS IN ENGLAND AND SCOTLAND

The death rate from respiratory tuberculosis in England and Wales is now only one-quarter of the rate of one hundred years ago. At that time the death rate for females was higher than that for males, but because it fell more rapidly it is now lower than the male rate. In 1851–60 the standardized death rate for males was 2,694 and for females 2,854 per million ; in 1921–30 the figures were 868 for males and 677 for females. The death rate for both sexes continued to decline until 1939, when the war interrupted the trend and the rate began to increase. The peak was reached in 1941, but after remaining at a high level for two years the rate fell, and in 1946 and 1947 it was below the pre-war figure. The death rate from non-pulmonary tuberculosis has followed a similar but not parallel trend. The speed of decline was slower at first, but since the beginning of the century the fall has been faster for non-pulmonary than for pulmonary tuberculosis. Again there was a rise during the early war years, but since then the rate has declined more rapidly than that for respiratory tuberculosis. The comparative mortality index for non-pulmonary tuberculosis in 1947 was only three-quarters of the 1938 value, while the index for respiratory tuberculosis was slightly over nine-tenths of the 1938 value.

Judged from the trend of the death rates the present position appears to be satisfactory, and a continued fall in mortality might safely be expected. But a doubt is cast on this prediction by the notification figures. The number of new cases diagnosed rose from 40,742 in 1938 to 47,186 in 1947. How far this signifies a true increase in the incidence of tuberculosis is problematical. It may be due, in part at least, to more strenuous efforts to diagnose and control the disease : the large decrease in notifications, almost 2,000, recorded in 1940 indicates that notification is related to the facilities for diagnosis and treatment. The greater number of notifications may also be partly due to mass radiography. Many minimal lesions have been found that would otherwise have escaped detection. It is impossible at present to estimate in what proportion of these cases the infection becomes clinically active during observation, but it should be possible to answer this question during the next few years. The higher number of notifications probably does not signify an actual increase in incidence. But there has been no falling off of the number of deaths from tuberculosis of persons not notified before death. In fact there has been in recent years a slight increase ; the numbers not notified before death were 3,468, 3,603, 3,580, and 3,682 for the four years 1944–7. In 1947 13% of the persons dying from respiratory tuberculosis were not notified during life ; in 1938 the figure was 9%.

The proportion of tuberculous patients being treated in institutions in 1947 was 2% more than in 1946 ; but the demand for hospital beds had not been met, and the delay in admission had increased. In the first quarter of 1947 there were 32,586 beds provided, of which 4,618 were temporarily not in use—mainly because of lack of staff. The situation improved during the year, and in the last quarter the percentage of beds available but out of use dropped from 14.2 to 11.5. This was, however, offset by the rapid increase in the numbers on the waiting-list. In the first quarter of 1947 6,882 persons were awaiting institutional treatment, and by the last quarter the number had gone up to 8,269. Adequate staffing of all available beds would reduce the number on the waiting-list by almost one-half. The rise in the numbers awaiting admission may be due partly to the fact that modern treatment necessitates a longer stay in hospital, partly to a real

increase in incidence, or partly because patients are placed on the waiting-list in an earlier stage of the disease, with the result that there is a smaller loss through deaths before admission. Whatever the cause, or combination of causes, there are not enough beds.

In Scotland the trend of the death rate from tuberculosis has been similar to that of England and Wales, though the figures have been consistently higher. The rate did not start to decline so early in Scotland, but from 1866 it fell until 1939, when a rise occurred. Contrary to the post-war experience of England and Wales the tuberculosis death rate in Scotland failed to decline, the death rate from respiratory tuberculosis being 64 per 100,000 in 1946, 66 in 1947, and 66 in 1948—a reversion to the level of 20 years earlier. A few weeks ago in this *Journal* Mr. Walter Elliot[1] described the failure of the rate in Scotland to follow the same trend as the English rate as "a fascinating problem of public health to which no solution has yet been found." In a letter published in last week's *Journal* (p. 869) Dr. Ian Sutherland, of the Institute of Social Medicine at Oxford, compared the mortality from the disease in England and Wales and in Scotland by sex and age: in his opinion the statistical evidence indicates that "the mortality from pulmonary tuberculosis among young adults in Scotland compares very unfavourably with that in England and Wales, and is relatively much worse now than it was early in the war," and also that "the increase which has occurred since the war in the death rate from the disease among Scottish women aged 15 to 34 is a matter meriting the fullest investigation."

Notifications of respiratory tuberculosis in Scotland were diminishing in the pre-war years, but recently they have risen steadily each year, from 4,637 in 1939 to 8,010 in 1948, and are now at the same level as in 1921. The rate of increase exceeds that recorded in England and Wales. Despite the rapid rise in the number of notifications a large proportion of tuberculous persons escape notification during life; 530 (15%) of the 3,472 persons who died from respiratory tuberculosis in 1947 were notified only at or after death.

It is even more difficult to obtain a vacancy in a sanatorium in Scotland than it is in England. The number of available beds rose from 4,263 at the end of 1946 to 4,707 at the end of 1947, while those empty through lack of staff decreased from 742 to 572, but the waiting-list increased from 1,889 to 2,572 during these years—if there had been enough staff this would have been reduced by one-fifth. The number of staffed institutional beds available for the treatment of respiratory tuberculosis in Scotland is only about two-thirds of the estimated minimum requirement. While Scotland has its special difficulties it is plain that the control of tuberculosis presents fundamentally the same problems in England, Wales, and Scotland. As Sir Andrew Davidson, Chief Medical Officer of the Department of Health for Scotland, recently remarked,[2] "The present need is for full and adequate co-operation between the health officers and the hospital services." New methods of prevention and treatment are being rapidly developed, and it is essential that all doctors engaged in the task of eradicating tuberculosis should work closely together so that useful knowledge is disseminated with the shortest delay.

[1] *British Medical Journal*, 1949, **2**, 297.
[2] Ibid., 1949, **2**, 806.

CHEMOTHERAPEUTIC TREATMENT OF TYPHOID

The chemotherapeutic treatment of typhoid may be said to have begun in 1887 with the observations of Chamberland[1] that the vapours of certain essential oils—sweet marjoram, camphor, sandalwood, and cloves—had an inhibitory action on the growth of typhoid bacilli. The earlier sulphonamides appeared to give some protection to mice against multiple lethal doses of *S. typhi* and *S. paratyphi B*,[2] but Britton[3] was unable to detect any bacteriostatic or bactericidal action *in vitro* on the growth of these organisms by sulphanilamide or allied drugs, and in human infections results were contradictory. With the discovery of the action of sulphaguanidine and sulphasuxidine on the organisms of bacillary dysentery hopes were raised that a cure for typhoid also might be in sight, but though abdominal discomfort was sometimes reduced the fever and general course of the infection were uninfluenced. With penicillin the same story was repeated: occasionally good results were obtained, but more often they were similar to those reported by Riser and his colleagues,[4] who found that in one chronic typhoid carrier bacteriological tests became negative after a total dose of 2,200,000 units, and in a second they became negative after 2,650,000 units but relapsed one week after the drug had been stopped. Streptomycin *in vitro* appears to inhibit the growth of *S. typhi* in concentrations of from 1 to 16 units per ml., but in man the results are unimpressive. Of 11 patients with *S. typhi* or *S. paratyphi A* infections, including three carriers, treated by Pulaski and Amspacher,[5] nine recovered and only two died, but in the six cases where *S. typhi* was the causative organism there was no real evidence that streptomycin had shortened the course of the infection. It was concluded that parenteral streptomycin alone was useless, but that possibly combined oral and systemic penicillin might be of value.

Very much more encouraging results have been obtained with chloramphenicol ("chloromycetin"), which was first used in Malaya by Woodward and his

colleagues[6] almost as a by-product of their investigations on scrub typhus. We have already drawn attention to these studies[7]: 10 patients were successfully treated, though two relapsed after afebrile periods of 10 and 16 days and one had a haemorrhage. The average total dose was 19.1 g. per patient, given over an average period of 8.1 days. Both the patients who relapsed were cured by further chloramphenicol. These preliminary results have been amply confirmed. Murgatroyd[8] reported one dramatic recovery in this *Journal*: a total dosage of 22.75 g. was given. Bradley[9] gave preliminary findings relating to the use of the drug during an epidemic in Berkshire in which an attempt was made to obtain an unbiased result by treating alternate cases: the change in the constitutional symptoms was remarkable, though three of nine patients relapsed. Among all those treated with chloramphenicol in this outbreak four only relapsed, and these responded to further doses of the antibiotic. Douglas[10] treated two cases, in one of which administration of chloramphenicol was begun on the third day of illness. The dose was 4 g. in the first hour, 0.25 g. two-hourly until the patients were afebrile, and then 0.25 g. four-hourly until a total of 20 g. had been given. Four days after beginning treatment the temperatures were normal, but though blood cultures on the second, third, and fourth days were negative *S. typhi* was present in the stools until the sixth day. There were no relapses. In this issue of the *Journal* Dr. W. Lomax describes the successful treatment of a severe infection which the patient contracted in Egypt and which developed on the voyage to England. From the U.S.A. Foster and Condon[11] record complete remission of the temperature in 96 hours in a patient who had shown no change after streptomycin therapy for four days. In Syria Kiledjian[12] successfully treated three patients infected with *S. typhi* and one with *S. paratyphi B*, and from Transjordan Tutunji[13] reported good results in two girls with *S. typhi* infections. No relapses were recorded. Shah[14] and Vakil[15] in India describe the use of chloramphenicol in series of 33 and 14 cases, though since blood cultures were not always performed it is uncertain how many of these patients were actually suffering from typhoid. Elsewhere in this issue Drs. J. C. Patel, D. D. Banker, and C. J. Modi, of Bombay, describe a series of six cases in which the blood cultures were all positive. As noted by other workers, the constitutional symptoms improved before the fall in temperature, which occurred very frequently in two stages—an initial reduction being followed by a rise and then by a slower subsidence. One of the six cases relapsed. In Egypt El Ramli[16] found that of 17 patients treated with chloramphenicol nine relapsed, whereas among 122 previous cases treated with other drugs only 16 had relapsed. In a series of 45 cases treated in Port Said and as yet unpublished there were only two relapses. The largest series of cases so far recorded is that by Musotto,[17] who describes a water-borne outbreak of typhoid at Pozzallo, near Ragusa, in which some 500 cases occurred. Unfortunately in his preliminary account he gives no precise figures, but all severe cases were treated with chloramphenicol and excellent results were obtained. The initial dose was 50 to 60 mg. per kg. of body weight in the first hour, capsules being given every 10 minutes, followed by a maintenance dose of 0.25 g. in adults and 0.12 g. in children every two to three hours. When the temperature had fallen to normal the same maintenance dose was continued four-hourly for at least five days. With this regime there were few relapses, and these promptly responded to further chloramphenicol. One patient who had an intestinal perforation recovered.

Comparatively few cases of paratyphoid infection have so far been treated. In Musotto's series there were a number of paratyphoid A infections which apparently responded satisfactorily. Montuschi[18] treated one case of paratyphoid B which reacted somewhat slowly: the temperature did not fall till the fourth day of treatment after 0.5 g. had been given three-hourly for 24 hours. Christie[19] briefly refers to eight cases of paratyphoid of unspecified type. One child died after six days' treatment with chloramphenicol; in most of the seven other cases the temperature became normal after four to five days, though one patient was afebrile in 48 hours. This result is no better than that in children treated on conservative lines, though it is mentioned that in another series of 10 children to whom no antibiotic was given pyrexia persisted for from nine to 15 days. It is thus possible that paratyphoid infections react less

[1] Chamberland, *Ann. Inst. Pasteur*, 1887, **1**, 153.
[2] Buttle, G. A. H., Parish, H. J., McLeod, M., and Stephenson, D., *Lancet*, 1937, **1**, 681.
[3] *Brit. J. exp. Path.*, 1938, **19**, 140.
[4] *Amer. J. med. Sci.*, 1946, **212**, 331.
[5] *Bull. U.S. Army med. Dept.*, 1947, **7**, 101.
[6] *Ann. Intern. Med.*, 1948, **29**, 131.
[7] *British Medical Journal*, 1949, **1**, 672.
[8] Ibid., 1949, **1**, 851.
[9] *Lancet*, 1949, **1**, 869.
[10] Ibid., 1949, **2**, 105.
[11] *J. Amer. med. Ass.*, 1949, **141**, 131.
[12] *Lancet*, 1949, **2**, 629.
[13] Ibid., 1949, **2**, 629.
[14] *Indian Physician*, 1949, **8**, 192.
[15] Ibid., 1949, **8**, 185.
[16] El Ramli, A. H., 1949: quoted by El Borolossy, A. W., and Buttle, G. A. H., *Lancet*, 1949, **2**, 559.
[17] *Il Policlin*, 1949, **56**, 1026.
[18] *Lancet*, 1949, **2**, 675.
[19] *Post-Grad. med. J.*, 1949, **25**, 409; *J. Mt. Sinai Hosp.*, 1949, **16**, 71.
[20] *British Medical Journal*, 1949, **1**, 943.
[21] Aureomycin in Typhoid Fever. Rept. to the Therapeutics Trials Committee *Ind. Res. Fund. Ass.*, 1949.
[22] *J. Amer. med. Ass.*, 1949, **141**, 129.
[23] *Lancet*, 1946, **1**, 81.
[24] *Z. Hyg. InfektKr.*, 1949, **129**, 119.
[25] *Lancet*, 1949, **2**, 559.
[26] Ibid., 1946, **2**, 114.
[27] Comerford, C. H., Richmond, H., and Kay, W. W., ibid., 1946, **2**, 343.
[28] El Ramli, A. H., and El Borolossy, A. W., quoted by El Borolossy, A. W., and Buttle, G. A. H., ibid., 1949, **2**, 559.
[29] Banks, H. S., in *Diseases of Children*, 1949, p. 863. Edited by Paterson, D., and Moncrieff, A. London.
[30] Bevan, G., Evans, R., Pugh, I., Sudds, M. V. N., Parker, M. T., and Sladden, A. F. S., *Lancet*, 1948, **1**, 545.
[31] Parsons, C. G., ibid., 1948, **1**, 510.
[32] Fry, R. M., Jones, R. E., Moore, B., Parker, M. T., and Thomson, S., *British Medical Journal*, 1948, **2**, 295.
[33] *J. Bact.*, 1945, **49**, 193.

readily to chloramphenicol than does typhoid. Further investigations are obviously necessary.

From published reports it appears that chloramphenicol does not readily induce drug-fastness, a point greatly in its favour. It is very nearly free from toxic effects, though Musotto and Patel and his colleagues refer to eczematous skin rashes. Ramli mentions anorexia, stomatitis, glossitis, mental apathy, and skin rashes. The most frequent complaint is of slight nausea, but it should be emphasized that reactions are both rare and mild. The greatest drawback to chloramphenicol is that in the doses used it is often bacteriostatic rather than bactericidal. This is borne out by Rumball and Moore,[20] who gave a chronic typhoid carrier, a boy 9 years of age, 10.5 g. in seven days without any effect on the presence of *S. typhi* in the stools: a further course of 5.25 g. in seven days caused the stools to become negative, but two days after treatment had ceased the organisms were again being excreted.

Since chloramphenicol in the doses so far used cannot be guaranteed to destroy all typhoid organisms in the body, three further methods of treatment have been explored. Other recently discovered antibiotics have been tested: aureomycin was given by Musotto to six patients, but the diarrhoea and vomiting were such that it had to be stopped. In India, Patel and his colleagues[21] also found aureomycin of no value. Polymyxin has been tried in five cases and found to be useless.[19] The administration of chloramphenicol for a longer period has been recommended. Smadel and his colleagues,[22] who incidentally find that synthetic chloramphenicol is quite as effective as the natural form, now recommend that the antibiotic should be given for not less than nine and not more than 14 days. Thus of 13 patients treated for eight days or less (average 6.9 days) seven relapsed; of 19 patients treated for nine to 14 days (average 11.2) none relapsed; and of 12 patients treated for 14 to 23 days (average 18) none relapsed. The total dose of chloramphenicol in the three groups averaged 13.5, 13.7, and 20.8 g. respectively. The dosage now recommended is 4 g. (16 capsules) in the first hour, followed by 1.5 g. (six capsules) twice daily till the patient becomes afebrile; then 0.75 g. (three capsules) twice daily for one week. The administration of the drug twice daily is less disconcerting for the patient and makes for easier nursing.

The third method which is being investigated is that of combined therapy. A synergistic action between penicillin and sulphonamides on *S. typhi* in mice was reported by Bigger[23] and has been confirmed by Knapp[24] and by El Borolossy and Buttle.[25] Advantage has been taken of this phenomenon in the treatment of typhoid in man by McSweeney,[26] but while some observers have obtained good results[27 28 29] others have entirely failed to demonstrate any synergistic effects.[19 30 31 32] The explanation for this divergence is that various strains of typhoid bacilli vary greatly in their sensitivity to penicillin. A similar synergistic action was found in mice by El Borolossy and Buttle with sulphadiazine and chloramphenicol. In human cases a combination of sulphathiazole and chloramphenicol might possibly be preferable to sulphadiazine and chloramphenicol, though it should be noted that Schweinburg and Yetwin[33] found *in vitro* that sulphamezathine is more bactericidal and bacteriostatic than sulphadiazine against *S. typhi*. There is thus a possibility that synergistic treatment of human typhoid infections with chloramphenicol and a sulphonamide may overcome the tendency to relapse characteristic of insufficient dosage with chloramphenicol by producing a rapid bactericidal effect.

THE ARTIFICIAL KIDNEY

In spite of much effort and ingenuity it is fair to say that the artificial kidney is still only an ideal and not an accomplished fact. In the opening pages of this issue Drs. Gordon Murray and E. Delorme and Mr. N. Thomas describe one form of "artificial kidney"; similar devices have been used by Kolff[1] and Alwall.[2] In all of them heparinized blood is led through a long cellophane tube immersed in a bath of fluid in which salts of sodium, potassium, calcium, and magnesium have been dissolved to simulate the electrolyte pattern of normal plasma. The cellophane membrane allows the passage of urea, electrolytes, and water, but not of protein or of red cells; as the blood flows along urea diffuses out into the bath fluid, while electrolytes diffuse outwards or inwards depending on whether their concentration in the actual plasma is greater or less than that in the "ideal plasma ultrafiltrate" of the bath fluid. In this way the blood leaves the apparatus having lost some of its diffusible non-protein nitrogen and having had its electrolyte composition restored to a somewhat arbitrary "normality."

The principle is simple enough, but its translation into practice brings difficulties to the doctor and real hazards to the patient. If the cellophane tube is made long enough to allow the dialysing process to be anything like complete, then the arterial blood pressure becomes an inadequate driving force and some sort of pump has to be introduced into the apparatus. Kolff uses a helical pump, having found a satisfactory way of joining the stationary tube in a vein to the tube wound round a rotating drum. Murray and his colleagues incorporate a syringe pump with rubber inlet and outlet valves, and claim that the use of large amounts

[1] *The Artificial Kidney*, 1946, Kampen, Holland.
[2] *Acta med. scand.*, 1947, **128**, 317.
[3] *Arch. intern. Med.*, 1949, **83**, 528.
[4] *Amer. J. Med.*, 1949, **7**, 45.
[5] *Lancet*, 1949, **2**, 229.
[6] Fine, J., Frank, H. A., and Seligman, A. M., *Ann. Surg.*, 1946, **124**, 857.
[7] Black, D. A. K., and Stanbury, S. W., *British Medical Journal*, 1948, **2**, 1101.

of heparin will prevent clotting on the valve flaps. Again, if the tube is long its internal volume may be appreciable in relation to the volume of blood which can be safely withdrawn, however temporarily, from the patient. The authors overcome this difficulty by "priming" their apparatus with suitable blood. Besides such difficulties, which are inherent in the apparatus, there are the further dangers of haemorrhage in a patient whose blood has to be made incoagulable by heparin throughout the period of dialysis. Also the anuric patient cannot protect himself against dehydration or water overload, and these may easily arise if the composition of the bath fluid is unsuitable.

The dangers of the artificial kidney are admitted by its makers and users, but they argue that acute renal failure is so serious a condition that desperate measures may be justified. This contention is based on the assumption that acute renal failure carries a very grave prognosis, and figures can be found which support this view. Several critical surveys have lately appeared, however, which show that the high mortality of anuria is largely attributable to faulty treatment, and that conservative treatment gives good results provided that excessive amounts of fluid are not given. Muirhead and his colleagues[3] found that renal function recovered spontaneously in most patients with anuria "provided they are not overloaded with salt and water in the vain attempt to stimulate urine production." Similar results were reported by Stock,[4] who found that the mortality in 22 patients with anuria was only 50% and that in the majority of the 11 fatal cases fluid overload was a more important feature than nitrogen or other retention. Even more convincing is the experience of Bull and his colleagues[5] at the London Postgraduate School, who have advisedly given up the use of the artificial kidney in favour of a high-calorie low-protein diet and a controlled fluid intake of a litre per day. They have had good results with this regime, and it can be safely carried out by those who lack the technical knowledge and fortitude to maintain a patient on the artificial kidney.

It seems clear that until artificial kidneys become safer they have no place in the treatment of acute renal failure. To say this is not to suggest that the work done in this field has been wasted or that it should not continue. Already the excretory functions of the kidney can be artificially performed for a short time, not only by the various forms of artificial kidney but also by such expedients as peritoneal irrigation[6] or intestinal intubation.[7] All these methods require the use of large volumes of irrigating fluid, since the excreting surfaces have no power to concentrate metabolites; they can therefore be used only in special clinics, where a close watch can be kept on the electrolyte composition of the plasma. So far no artificial method has been found for performing the homeostatic, as opposed to the excretory, functions of the kidney. This is a serious matter, for while it is logical to suppose that continued failure of renal excretion would cause death, the observed facts indicate that in acute anuria immediate danger arises from the patient's lack of any effective defence against overloading with water and salt. Bull and his colleagues[5] believe that water intoxication is a real risk in such patients. When patients with anuria have already been maltreated by large infusions, a policy of deliberate and controlled dehydration may be indicated, and intestinal perfusion with 5% lactose, as used by Brun in Copenhagen, may be a suitable way of doing this.

ASTHMA

Reports on the value of antihistamine drugs in asthma have, on the whole, been disappointing.[1-5] Their failure, however, is only relative in comparison with the great relief of symptoms which these drugs give in some cases of acute urticaria and hay-fever, in the treatment of which they have a permanent place. Most observers claim that in the symptomatic treatment of asthma the antihistamine drugs can be of value.[2-6] Elsewhere in this issue Dr. H. Herxheimer substantiates these claims and gives particulars of the partial relief of artificially induced and naturally occurring attacks of asthma afforded by various antihistamine drugs. In the routine treatment of asthma they are especially useful in preventing nocturnal attacks, and in this respect they seem to be superior to ephedrine or adrenaline analogues both because of their sedative side-effect and because some at least continue to exert their action for a much longer period of time. Even so, their value in asthma is limited. In some of Herxheimer's cases the antihistamine drugs were quite ineffective, severe attacks of asthma not being controlled even after large doses. Moreover, though the vital capacity was often notably increased, in no case was it restored to the maximal, and therefore presumably normal, figure for the patient. It may be that with newer, more potent preparations, less apt to cause unpleasant side-effects, better results will be obtained. At the moment the place of antihistamine drugs in the treatment of asthma must remain *sub judice*.

Some observers have pointed out that these drugs are valueless in the presence of bronchial infection or nasal abnormality.[2 5] It is indeed not surprising that the response to treatment varies considerably. On the evidence available few would maintain that asthma is invariably caused by the action of histamine on the bronchioles, or even agree with Drs. E. O. and G. E. O. Williams, whose paper on the natural history of asthma appears in this issue at page 897, that it is always due to bronchiolar spasm: oedema of the submucosa probably plays an almost equally important part. These authors emphasize the variation in aetiological and aggravating factors in asthma, the absence of any clear-cut relationship between them, and, by implication, the present ignorance of the essential pathogenesis. Most of the factors commonly regarded as of aetiological importance act merely as detonators which explode the hidden charge, thus converting the latent into the overt asthmatic.

Williams and Williams bring evidence to show that the onset of asthma and of subsequent attacks is in some cases definitely related to the disturbances associated with

[1] Hunter, R. B., and Dunlop, D. M., *Quart. J. Med.*, 1948, n.s. **17**, 271.
[2] Levin, S. J., and Moss, S. S., *J. Pediat.*, 1949, **34**, 616.
[3] Waldbott, G. L., and Young, M. I., *J. Allergy*, 1948, **19**, 313.
[4] Serafini, U., ibid., 1948, **19**, 256.
[5] Sternberg, L., and Gottesman, J., *Ann. Allergy*, 1948, **6**, 569.
[6] Herxheimer, H., *Lancet*, 1948, **1**, 667.
[7] Zondek, B., and Bromberg, R. M., *J. Obstet. Gynaec. Brit. Emp.*, 1947, **54**, 1.
[8] Baer, R. L., Witten, V. H., and Allen, J. R., *Ann. Allergy*, 1948, **6**, 239.
[9] Flensborg, E. W., *Acta paediatr., Stockh.*, 1945, **33**, 4.

pregnancy and menstruation. Such observations are of course not new, but evidence is accumulating that sensitization to endocrine products may cause asthma.[7 8] If this is so, and more information must be collected before such a view can be accepted, the whole field of autosensitization as a cause of asthma must be re-explored. In summing-up the evidence, it must be remembered that pregnancy often exerts a beneficial effect in chronic asthma, and that psychological disturbances which may be of aetiological importance occur commonly during pregnancy and menstruation. Another significant observation is that eleven out of sixty-four patients followed up for a period of from 7 to 12 years had died, six as a result of their asthma. Flensborg recorded a mortality of 5% in a group of children seen between 1926 and 1939.[9] Asthma not only cripples, it can also be a killing disease.

INSULIN REQUIREMENTS

Newspaper reports of scientific work are seldom sufficiently detailed or accurate to make it possible to express any opinion on the merits or conclusions of the work described. In the *New York Times*[1] there recently appeared an article by William L. Laurence in which are summarized studies carried out on 4,000 diabetic patients over a period of 14 years by a group of chemists and physicians of the Jewish Hospital of St. Louis, headed by Dr. Michael Somogyi. These workers are said to have come to the remarkable conclusion that provided proper attention is paid in treatment to dietary control 99% of adult diabetics do not require insulin. The essence of such control appears to be the reduction of weight to the ideal level and the dietary restriction of fats—protein and carbohydrate apparently being allowed in liberal amounts. The scientific arguments, as reported, need not be considered at this stage, and in the absence of detailed case reports no conclusions can be drawn about the validity of the remarkable claim made by Dr. Somogyi and his co-workers. The statement that less than 1% of adult diabetics require insulin is, however, so contrary to the experience of workers throughout the world, including the U.S.A., that it should not be accepted without very careful study of the evidence on which it is based. Until such evidence is available both diabetics and those who treat them will be wise to adhere to the generally accepted principles of treatment which are based on considerably more than 14 years of intensive study and research on many thousands of cases of diabetes. If Dr. Somogyi and his colleagues have only discovered that there is a large group of obese diabetics in whom a reduction in weight is the most effective form of treatment and in whom insulin is not only unnecessary but usually contra-indicated, then nothing new has been added to our knowledge of the treatment of diabetes. If, on the other hand, as the article in the *New York Times* suggests, the conclusions apply also to the young adult with severe diabetes, the whole conception of insulin therapy in diabetes will have to be readjusted and the importance of Banting and Best's great discovery reassessed; it is unlikely that time will prove this to be necessary.

[1] *New York Times*, September 19, 1949.

WMA

An account of the proceedings of the General Assembly of the World Medical Association is published in this week's *Supplement*. From this it will be seen that the interest of this new body extends over a wide field of medicine—medical ethics, international medical congresses, hospitals, pharmacopoeias, postgraduate education, and social security. Perhaps the most interesting debate was on the last item based on the report of a committee of which Dr. Charles Hill was chairman. This report presented a factual summary of the conditions now existing in 24 countries. Dr. H. Guy Dain summarized for the foreign visitors what he called the teething troubles of the National Health Service. Our colleagues from other countries were restrained in their criticism of the system adopted in Britain, but those who spoke did not consider that the British N.H.S. was the final solution to the problem of providing medical care. Dr. Paul Cibrie, for example, considered that the capitation method of paying the doctor put him at the mercy of his patient. Dr. W. Magner said that while the Canadian Medical Association approved the principle of contributory health insurance it would oppose any Act modelled on the British Act. For the U.S.A. Dr. W. Cline told how in his country the medical profession were developing and enlarging the voluntary insurance system, and considered that the care of the indigent was the responsibility of the local community. Dr. S. C. Sen gave some idea of the tremendous problems facing India when he observed that for a population of 350 million there were at present only about 50,000 qualified doctors.

The position of the general practitioner in medicine is evidently causing concern abroad as well as at home. The view was expressed that in these days there was a tendency to look down upon the general practitioner, and Dr. Dag Knutson observed that if the general practitioner accepted an economically lower status than the specialist he would continue to be looked down upon. There was some discussion on a proposition in one of the committee reports about the work of general practitioners in hospitals, and the Assembly approved of the suggestion that general practitioners should be integrated into the Hospital Service. Dr. Fishbein pointed out that the tendency of medical progress was to give the general practitioner the opportunity of treating cases that formerly went to the specialist. The development of medical services is closely linked with the work and status of the general practitioner, and it seems likely that these two problems will come to the fore in the discussions held by the WMA during the coming year.

It has been announced in Oslo that the Nobel Peace Prize for 1949 has been awarded to Lord Boyd-Orr, M.D., F.R.S., Chancellor of Glasgow University, and formerly Director-General of the United Nations Food and Agriculture Organization. Sir John Boyd-Orr, as he then was, was created a Baron at the beginning of this year. In Stockholm last month he was re-elected President of the World Movement for a World Federal Government. The Nobel Peace Prize is said to amount to £7,815 at the present rate of exchange.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

THE ACUTE EAR

BY

W. M. MOLLISON, F.R.C.S.

Consulting Surgeon, Ear and Throat Department, Guy's Hospital

The cardinal symptoms of ear disease are earache, deafness, vertigo, and tinnitus. Any of these symptoms, if of acute onset or if severe, might be called an "acute ear." This article will deal only with acutely painful affections of the external and middle ear. The pain is, in the majority of cases, inflammatory, but in a small minority no local lesion is to be found in the meatus or tympanic membrane.

To decide whether the site of pain lies in the external or middle ear it is essential to examine the ear carefully. The electric auriscope affords the easiest view, especially if the patient is a child or is in bed. The skin of the meatus is normally pale pink, and the presence of the speculum should cause no discomfort. The tympanic membrane can be seen at a distance of about one inch (2.5 cm.) from the concha. Since the ceruminous glands and hair follicles occupy only the outer two-thirds of the meatus, infections—e.g., boils—occur only in this area.

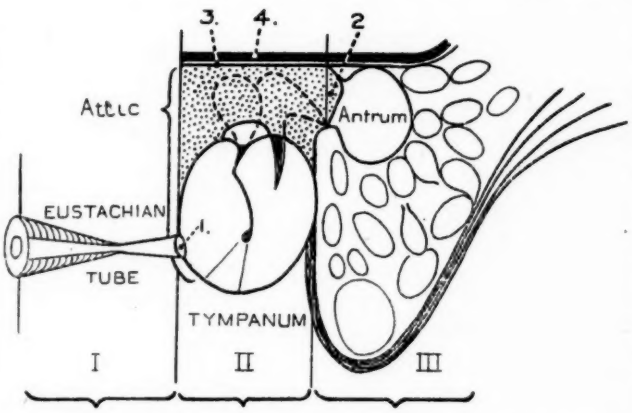
Acute Infections of the External Ear

The Pinna.—The pinna is subject to the same infections as other parts of the skin and does not come within the compass of this article.

The External Auditory Meatus.—Furunculosis, or boils in the glands or hair follicles of the outer two-thirds of the meatus, is an extremely painful condition. At an early stage the boil may be too small to produce any swelling and can be diagnosed only by the presence of an area of red skin and the discovery of a tender spot by a probe. Later, an obvious tender swelling or swellings simplify the diagnosis.

The lymphatics of the meatus drain to glands (1) in front of the tragus, (2) behind on the surface of the mastoid process, and (3) below the tip of the process. Tenderness in any of these positions is an aid to diagnosis. Lymphangitis may occur as a complication. The swelling to which it gives rise is over the mastoid process and is often sufficient to push the pinna forward and downwards. It pits on pressure and may raise a suspicion of acute mastoiditis with subperiosteal abscess. The type of tenderness differentiates between the swellings—that of lymphangitis is superficial, and if pressure is maintained the bone can be reached without causing any increase in pain; in the case of mastoiditis, on the other hand, the harder the pressure the worse the pain.

No loss of hearing occurs in furunculosis unless the boils are extensive enough to block the meatus; even then a narrow speculum insinuated between the boils will restore hearing to normal.



1. Opening of tube into tympanum. 2. Aditus—opening from attic into the antrum. 3. Plate of bone forming the roof of attic in front and of the antrum behind; it is also the floor of the middle cranial fossa. 4. Dura mater.

Treatment of Furunculosis

The meatus, including that part deep to the boil, must be kept clean and dry. Every otologist has favourite drugs for this purpose, either in the form of drops or for application on gauze wicks. Well-tried prescriptions are:

Glycerin of phenol and glycerin, equal parts.
Saturated solution of magnesium sulphate, with or without glycerin.
Ichthyol in glycerin (10%).
Gentian violet in spirit (2%).
Silver nitrate (10%).
Aluminium acetate (8%).
Penicillin drops should not be used.

Incision should only be employed when a furuncle shows pus at its apex, though rupture of the boil may be hastened by the application of a minute drop of pure carbolic acid. The application of warmth is comforting, and an electrically heated pad is satisfactory for the purpose.

Although a course of sulphonamide may effect a dramatic cure, the fact that so many different drugs have been advocated is an index of the unsatisfactory results of treatment of this most painful affection.

Acute Infections of the Middle Ear

Any acute infection of the upper respiratory tract involves the nasopharynx and may spread to the Eustachian tube and so to the middle ear.

Anatomy.—The middle-ear tract extends from the nasopharyngeal end of the Eustachian tube, through the tympanum or middle ear, and thence through the aditus to the mastoid antrum to the air cells in the mastoid process. The tract may be conveniently divided into three parts: (1) The Eustachian tube, (2) the middle ear or tympanic cavity, and (3) the mastoid antrum and mastoid cells (see Figure). Inflammation may be mainly confined to part 1, or to parts 1 and 2, causing acute otitis media. Inflammation can spread from here through the aditus to the mastoid antrum. It is probable that some inflammation develops in the antrum in most cases of acute otitis media, and in suppurative cases the mastoid cells become involved to produce acute mastoiditis. In the case of severe haemolytic streptococcal or pneumococcal infections the whole tract may be rapidly involved.

The infecting organism is usually a streptococcus, but may be a staphylococcus or pneumococcus. Some specific fevers, notably measles, scarlet fever, and diphtheria, as well as influenza, may lead to acute otitis media. Paranasal sinusitis may supply the infection, and fresh-water bathing and the presence of adenoids are sometimes contributory causes.

Symptoms and Signs of Acute Otitis Media

Local Symptoms.—Earache is severe and of a stabbing character, with intermissions. Deafness is always present, but varies in degree.

General Symptoms.—Toxaemia, loss of appetite, malaise, rise in temperature to as much as 104° F. (40° C.) in children or 100° F. (37.8° C.) in adults.

Signs.—As the tympanic membrane is the only part of the middle ear that can be examined, recognition of the changes occurring in it are important. Normally the membrane has a pearly colour, is shiny, and slightly concave. In the early stages of inflammation a sheaf of tiny vessels is seen running immediately behind the malleus; small vessels directed towards the centre of the membrane also become apparent at the periphery. The posterior part soon becomes red. The next stage is bulging of the membrane, at first in the posterior part but later affecting the whole structure. Finally, if there is no surgical interference, rupture takes place and the blood and serum are discharged. Should the infection be mild, resolution may occur in the earlier stages and the discharge last for a day or two only. The rapidity with which these changes take place is to a great extent an indication of the severity of the condition.

Drug Treatment

It is a truism to state that chemotherapy and antibiotics have changed the picture of acute infections, and therefore of acute otitis media, but it is equally correct to point out that best results can only be achieved by early and adequate dosage. It must also be realized that these drugs do not replace surgery, but aid recovery and go far to prevent complications.

The choice of drugs lies between the sulphonamides and penicillin. It has been suggested that the former should take first place and penicillin be reserved for cases that fail to respond. Whether sulphadiazine, sulphamezathine, or any other alternative is chosen, 2 g. (four tablets) are given as a first dose, and thereafter 6 to 8 g. in equal doses in the following 24 hours. In the case of children half these doses are to be used, or dosage given on the scale of 0.15 g. per kilo body weight. Treatment is continued for four or five days.

Penicillin.—The preparation of choice is procaine penicillin (an oily preparation with aluminium stearate), since this has the advantage of maintaining a therapeutic blood level in 80–90% of patients for 24 hours. One ml. of this preparation contains 300,000 units of penicillin. Injection is intramuscular and is given daily for as long as necessary. Should a watery solution of penicillin be used, 500,000 units should be given twice a day for at least four days. This treatment must be instituted as soon as the diagnosis has been made by observation of the red appearance of the membrane.

Surgical Treatment

Should the membrane continue to appear red after 48 hours, should pain persist, or should the membrane bulge, the operation of myringotomy must be performed. If the membrane is bulging when the patient is first seen myringotomy should precede the administration of drugs. After spontaneous rupture and discharge, penicillin should be administered. If discharge from the ear continues for two weeks in spite of chemotherapy or penicillin the mastoid cells must be opened.

In the pre-sulphonamide days the diagnosis of acute mastoiditis, and therefore the indications for operation, rested on a sound basis of symptoms and signs—pain; continued, often profuse, purulent discharge; swinging temperature up to 99.6° F. (37.6° C.); toxaemia, deafness, and tenderness over the mastoid process; and in late cases swelling and redness of skin. If all these features were present the diagnosis was obvious. There were cases, however, in which some, or indeed most, of these signs were absent. Indication for operation then rested on deafness and the persistence of one other symptom or sign. This rule is still more important to-day, because sulphonamides and penicillin, though cutting short the acute otitis, have the drawback of masking the symptoms. Pain and fever cease and the patient feels well, but the disease may progress. In consequence some otologists forbid drug treatment, but this drastic step is unjustified if the rules concerning the indications for operation are strictly observed. The absence of typical symptoms and signs following drug treatment has been named "masked mastoid."

Continuance of any one symptom—e.g., pain, discharge, toxaemia, or even deafness alone—calls for operation. *X*-ray examination of the mastoids aids diagnosis, for the affected cells appear clouded when compared with those on the opposite side. Should operation not be performed in a case of masked mastoid because the patient appears to have recovered, the sudden occurrence of facial paralysis may reveal that the disease is progressing and requires immediate operation. Results are good, and the paralysis clears up in about three weeks.

It has been stated that intracranial complications of otitis are more common since drug treatment became almost universal. If this is so, it may be the result of reluctance to operate on the mastoid, or delay in doing so, in cases of apparent recovery. Sulphonamides have been accused of causing deafness, but some of the cases at least were due to unresolved middle-ear infection and would have been avoided by operation on the mastoid to drain the middle ear efficiently.

Acute Otitis in Infants

The problem of acute otitis in infants presents special difficulties, for the patients are unable to indicate the site of pain, and diagnosis is largely a matter of exclusion. The infant is ill and has a high temperature; he cries, refuses food, and may have diarrhoea and vomiting. Should the physician fail to find signs of abdominal or chest disease, or any local lesion, the ears must be considered as a probable cause of the illness. Even when changes in the tympanic membrane are minimal, myringotomy may release a small quantity of fluid or pus. If otorrhoea persists and the condition of the infant does not improve in two or three days the necessity of opening the mastoid arises. Infants tolerate injections of procaine penicillin, and by this means the prognosis is improved. Investigations have shown that injections of 300,000 units can be given to infants aged 1 to 5 days without causing disturbance or pain. This dose should therefore be administered to infants or young children found to be suffering from acute otitis media. The injection is made once a day. It is to be expected that this treatment will reduce the incidence of mastoid infection, but no figures are yet available.

In cases in which the infecting organism proves to be penicillin-resistant, streptomycin offers an alternative treatment.

Trauma

Rarely, an "acute ear" is the result of trauma. Accidental puncture of the membrane occurs from thorns, needles, hair slides, and hot or corrosive fluids entering the external meatus, and rupture of the membrane is a common result of near explosions.

Treatment must be directed to prevent infection. Syringing is to be avoided. Any debris should be wiped out with wool moistened with spirit and the meatus lightly plugged with sterile wool. Prophylactic injections of procaine penicillin may be given. Should infection and suppuration follow, the same rules apply as in the case of primary acute middle-ear infection.

A group of cases due to flying is also to be considered. Many fliers notice unpleasant sensations in the ears even when descending gradually, and if descent has been rapid some complain of severe pain. The ears usually become normal in an hour or so, but when pain and deafness persist inflation of the Eustachian tube or tubes generally relieves the patient. Politzerization, or self-inflation, is often successful. If not, the Eustachian catheter will be needed on a few occasions. Examination shows retraction of the membrane, which is often reddened. The condition is one of barotrauma.

FUNCTIONAL DIFFERENTIATION IN MAMMARY TUMOURS

The fifth Kettle Memorial Lecture was delivered at the Royal College of Surgeons on October 7, Mr. Lionel Norbury presiding, by Dr. Beatrice Pullinger, whose subject was the significance of functional differentiation in mammary tumours.

Dr. Pullinger said that she was one of the few of Kettle's students who, inspired by his courage and his love of pathology, and many other great qualities in him, persisted in their devotion to pathology in spite of his grim warning not to do so. His teaching and work were never limited to the descriptive field, but he had regretted that circumstances prevented him devoting his whole time to experimental pathology.

It was therefore fitting to recall Kettle's teaching with an account of what might be learned from an experimental study of functional differentiation in the mammary gland and its tumours. In the course of some experimental work the need arose to vary functional differentiation at will, and this had led to a quantitative study of such differentiation around the time of puberty. A few, not very successful, attempts had been made to measure the quantitative response of the mammary gland to hormones, mice being the test animals. She had been able, with the help of a colleague, to prove on a statistical basis that there was a quantitative relationship between dosage and response, but the precise relationship was variable, revealing a change in sensitivity the source of which had not been determined.

The mammary gland developed in response to comparatively few stimuli. Of the known stimuli oestrogen was surpassed only by its combination with progesterone. It was thought by some investigators that a product of the anterior pituitary also stimulated the growth of the mammary gland. The lecturer went on to mention certain types of pathological stimulus, and said that there was one which had so far eluded all research, starting and perpetuating the growth of adeno-carcinomas and squamous carcinomas. All traces of the Bittner agent were absent.

She then put forward a classification of different types of mammary tumours in mice according to type, agent, and morphological characteristics. It was known that heritable mammary tumours contained the Bittner agent, a virus-like entity, on which they were dependent for their growth and transmission. Viruses might be graded as fibroblastic, breaking up and destroying the cells; as passengers, causing neither harm nor benefit to the host cells; and as formative agents, combining with the cells to cause cell proliferation and their own reproduction. There was also the possibility that both oestrogens and virus excited an intracellular link to effect these changes, though that hypothesis would be difficult to prove.

Certain non-virus-containing tumours gave no clues to the nature of the stimulus to cell division, and yet were morphologically indistinguishable from those which contained virus. Either a positive stimulus or the removal of an inhibition must be looked for; she herself favoured a positive stimulus, and the responses to specific hormones were themselves pointers to the presence of such a stimulus. The elucidation of abnormal stimuli was a matter of great difficulty on account of the lack of knowledge of normal stimuli, but, assuming that nature was economical in her means, the specific hormones provided clues for experimental trial.

Preparations and Appliances

HEPARIN ADMINISTRATION BY POLYTHENE TUBING

Dr. W. A. L. MacFadyen, Royal Infirmary, Edinburgh, writes: It has been found possible to abolish the inconvenience, both to patient and medical staff, of repeated venepuncture in the administration of heparin by the use of indwelling intravenous polythene tubing and a special attachment. The apparatus required is shown in Fig. 1. The attachment (D) consists of a Record-fitting mount on to which is screwed a small hollow screw cap containing a replaceable rubber diaphragm (E). This has been specially made for the purpose by Archibald Young and Sons, Edinburgh. The tubing (A) is a length of the polythene cannula, size 1 (bore 0.5 mm.) of Allen and Hanburys. It has been found that this tubing can usually be threaded through a needle of bore B.W.G. 14 (B), but occasionally, owing to slight variations in the diameter of the tubing, a B.W.G. 12 needle may be required. Some 10–12 in. (25–30 cm.) of the tubing, having been found to slip easily through the introducing needle, is sterilized by boiling, with the precautions advocated by the makers. The attachment (D and E), having been sterilized and assembled, is filled with heparin (it requires only a fraction of 1 ml.) and attached to a sterile hypodermic needle (C) of such diameter that it is held firmly when inserted into the tubing. A needle of bore 15 S.W.G. is usually satisfactory. The tubing is filled with heparin and the initial dose of heparin injected into the chosen vein by means of a syringe and the chosen sterile introducing needle. The syringe is removed, the polythene tubing threaded through for 4–5 in. (10–12 cm.) into the vein, the introducing needle withdrawn from the vein and quickly slipped off the tubing, and the hypodermic needle with the special attachment quickly inserted into the free end of the polythene tubing. The point of entry of the tubing is sealed with collodion and covered with a sterile dressing, and the whole apparatus strapped down. It is helpful to tie a loose knot in the exposed portion of the tubing to prevent it slipping further into the vein. Succeeding heparin injections are then given by the nursing staff by means of a syringe and a fine intradermal needle, the latter being inserted through the rubber diaphragm. The nurse should be instructed that the syringe should contain no air and that she should not draw back the plunger after inserting the needle, since it is

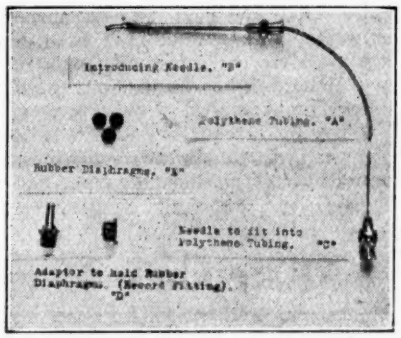

Introducing Needle, "B"
Polythene Tubing, "A"
Rubber Diaphragm, "E"
Needle to fit into Polythene Tubing, "C"
Adaptor to hold Rubber Diaphragm. (Record Fitting). "D"

Fig. 1.—Apparatus for intravenous administration of heparin.

desired to maintain a column of heparin unmixed with blood in the tubing and attachment.

Serial estimation of clotting time has shown that the polythene does not impair the anticoagulant effect of heparin. The apparatus has been used mainly for the initial administration of heparin to patients suffering from intravascular thrombosis for the period of two to four days before dicoumarol, simultaneously administered, has exerted its effect. It has also been employed effectively for much longer periods in patients in whom there existed a specific contraindication to dicoumarol therapy.

It is essential that the strictest sterile precautions are observed in the preparation and setting up of the apparatus. The tubing is most conveniently inserted at the antecubital fossa, where veins are most easily found (see Fig. 2). The patient is still able to flex the elbow and retains reasonable use of the arm. It is felt that the apparatus has considerable advantages over an indwelling intravenous needle, such as that described by Olovson (*Lancet*, 1948, 2, 495), in that it is more comfortable for the patient, allows free movement of the limb, and is not liable to require changing, since the polythene stimulates no foreign-body reaction. Furthermore, the special attachment is more easily cleaned and sterilized than the cumbersome indwelling needles that have been described. If polythene is not available the attachment can, of course, be inserted into any Record-fitting intravenous needle to serve as a simple indwelling apparatus.

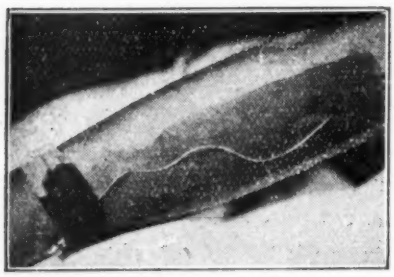


Fig. 2.—Intravenous polythene tubing in use. The skin has been painted with iodine to demonstrate the cannula more clearly. For the same reason the latter has been left longer than is necessary.

I wish to record my gratitude to Dr. A. Fergus Hewat, physician, Royal Infirmary, Edinburgh, for his kindness in permitting me to study the cases under his care.

Reports of Societies

PROGRESS IN OPHTHALMOLOGY

In his presidential address to the Section of Ophthalmology of the Royal Society of Medicine on October 13 Mr. Montague Hine said that this was a suitable occasion on which to stress the continued progress of ophthalmology. A similar review in a presidential address to the Section was given in 1926 by Mr. Ernest Clarke, who carried his story back to 1881 when he started ophthalmological practice. Mr. Hine took up the story from the point where Mr. Clarke left off. During these last 23 years, he said, treatment in many directions had improved, new operations had appeared or old ones had been perfected, and recently discovered remedies were being used with remarkable results. In addition much work had been done on the pathology and biochemistry of the eye, the full harvest of which had not yet been reaped.

The most spectacular advance in surgical treatment had been for detachment of the retina. The first Gonin type of operation at Moorfields was carried out in 1930. During the next year or two the means of obtaining a less localized reaction in the choroid and retina was sought for, and after some trial and error very weak diathermic currents were found to be most suitable, and these replaced the cautery in 1933. Since that time it could fairly be said that among unselected cases some 50% had been successfully treated, though a considerably higher figure—up to 75%—could be obtained if the material was of better quality and the operator more experienced. This was a very different story from the pre-Gonin days, when less than 1% of all detachments were successfully treated. It seemed almost a miracle that in the course of a few years after 1929 the treatment of detachment, from being one of the most hopeless procedures in ophthalmology, became one of the most hopeful. In 1926 in the Moorfields group the operations for detached retina by cautery puncture numbered only 20; in 1947 with the use of diathermy there were over 500 such operations.

Mr. Hine then touched on the treatment of squint, comparing the figures for 1926 and 1947. There was no doubt, he said, that orthoptic departments were of great assistance to ophthalmic surgeons and had influenced their views on operative measures. There were now 800 squint cases awaiting admission into the hospitals of the Moorfields group. He was rather surprised a few weeks ago to encounter a resident officer at one of the eye hospitals who confessed that he had never seen an excision of the lacrimal sac. In 1926, 96 cases of excision of the sac were recorded at Moorfields and 23 at the Royal Westminster Hospital; in 1947 the numbers were respectively 44 and 9, but in the latter year dacryocystorhinostomy—not a difficult operation—was carried out on 46 cases at the former hospital and 22 at the latter. The first record of this operation in the Moorfields reports was in 1932, but not until 1944 did it become the method of election among ophthalmic surgeons in this country and in America.

The development of corneal grafting dated from the experimental work of Tudor Thomas in 1930–4, and the first successful graft of a human eye in Great Britain was in 1933. Now this operation was undertaken by many ophthalmic surgeons. In 1947 five cases were operated on at Moorfields and four at the Royal Westminster.

Turning to contact lenses, he said that in 1926 it was only rarely that such a lens was ordered. Some few thousand contact lenses were now being made in Great Britain. The use of transparent plastic material for some optical appliances was a development of the last twenty years. Finally he made a brief mention of new drugs; the sulphonamides and penicillin had brought about an altered outlook in the treatment of eye infections.

Dr. Harold Levy, in proposing a vote of thanks, said that Mr. Hine had modestly omitted any mention of his own contribution to the treatment of detached retina, but it had been outstanding. During the 23 years which he had taken as the period of his review knowledge and treatment of ophthalmic disease had progressed out of all recognition, and there had also been a change, perhaps not so marked, in the nature of the cases which came to the out-patient department. The picture of the general affections of the eye which they saw thirty or forty years ago was not quite the same as it was to-day, thanks largely no doubt to better nutrition and to other social factors.

A recent circular from the Ministry of Health to hospital boards and committees outlines the procedure to be followed when they are threatened with legal actions. Proceedings should normally be brought against those bodies and not against the Ministry. If the Ministry is sued it should be informed at once, so that it may have the opportunity through the courts of having the appropriate board or committee substituted for the Ministry in the proceedings. In some exceptional cases it will be appropriate for the solicitor to the Ministry to act in the matter although the proceedings are being taken against a board or committee. The Ministry should be consulted on cases involving the construction of the Act and Regulations, in cases where an application is being threatened for leave to apply for a writ of mandamus, prohibition, or certiorari against the authority, and in cases involving questions of major legal importance. Authorities are not in general authorized to undertake the defence of hospital doctors sued in respect of alleged negligence. If it is sought to make an authority liable for negligent acts of a doctor it should take such steps as are open to it under the Law Reform (Married Women and Tortfeasors) Act, 1935, to obtain a contribution from him in respect of damages that may be recovered. In claims based on negligent treatment by a nurse it is expected that the authority will be sued as her employer, but if the nurse is joined in the proceedings the authority is authorized to see to her defence if she so desires.

Correspondence

Progress in Obstetrics

Sir,—In his enthusiasm to claim rights for the general practitioner that none would deny him, the writer of your leading article (October 8, p. 799) has loosed shafts at all and sundry. The barb directed at obstetricians for having abused caesarean section is both blunt and ill-directed. The medical schools are to be castigated if the new graduate is not "fully competent in obstetric technique"—and presumably surgical technique too. But further on in Dr. Haultain's papers, to which only carefully selected references are made in the leading article, it is pointed out that the student only learns sufficient to enable him to practise obstetrics *under supervision*, and therefore before undertaking domiciliary midwifery the new graduate should spend six months as a house-officer to a maternity unit. From a recent circular it would appear that the Central Health Services Council agree with Dr. Haultain in this.

At the time he wrote these papers Dr. Haultain envisaged that under the new Service the proportion of practitioners refraining from domiciliary midwifery would continue to increase. The speakers at the British Congress were "fearful" because the present regulations provide a financial inducement to the opposite effect. Moreover, the standard of antenatal supervision is dangerously low if two antenatal examinations suffice to qualify the practitioner for payment.

The writer of your leading article is obviously convinced that it is the aim of the obstetric specialist to oust the general practitioner from the sphere of midwifery. This is not true. It is his aim to see that the standard of domiciliary midwifery is kept high and that its practice is confined to those practitioners who are interested and well trained in the obstetric art. Nor does the specialist favour the midwife or encourage her in antagonism to the doctor, for it is obvious that the doctor must maintain his practice of normal midwifery if he is to recognize and treat the abnormal at the midwife's request.—I am, etc.,

Liverpool. S. Bender.

Sir,—The leading article entitled "Progress in Obstetrics" (October 8, p. 799) calls for a reply from a teacher in obstetrics. The adequacy of undergraduate teaching is constantly under consideration, and in this university centre as in others the quality of teaching has markedly improved and the quantity greatly increased during the 26 years which have elapsed since I did my student appointment in obstetrics.

Then we spent one month attending the hospital practice, not living in, and a second month attending district cases. I took 11 deliveries, a number at the time above the average, and most of them were on the district. The antenatal clinics at the hospital were not well attended, as less than one-third of the booked cases came regularly; they were for nine months of the year conducted by the resident tutor in obstetrics, a graduate of three years' standing. Only one member of the honorary staff shared in this work, of which she took charge during the remaining three months. Ward teaching and instruction on difficult deliveries were done almost entirely by the tutor, both on the mother and the baby. The tutor was a very good teacher, but we had next to no instruction from senior obstetricians.

Now students do a three months' appointment in obstetrics. During the last quarter the average number of cases taken by each student was 21. Throughout the appointment they live in a hostel adjoining the hospital. Each of the four obstetricians attends his own antenatal clinic each week, and the attendance of the booked patients is not far short of 100%. All emergency cases are written up by the students. There is ward teaching by the professor each week, and the other obstetricians teach in their duty weeks. The professor of child health and his staff conduct regular teaching on neonatal problems. The students obtain most of their cases in hospital, as the district is now much smaller than it was 25 years ago (about 300 cases a year instead of over 1,000). They get about three district cases each. The forceps deliveries, if difficult, are usually taken by a registrar who teaches on them; the easier ones are taken by the house-surgeons under supervision. Sometimes a student may be allowed to do one, but there are not enough for all to get one. It is better to let a limited number of people have a moderate experience, perhaps 10 cases, with the forceps than to let every student, including the potential anatomists, pathologists, and others, have just one each. We hope that most of the general-practitioner obstetricians of the future will have six months' resident experience in a maternity unit. The scheme of teaching is not perfect, but it has steadily improved.

If anyone thinks that it is possible to turn out a competent obstetrician after three months' student instruction he cannot have given a great deal of thought to the question. At the time when I qualified there were in the country large numbers of experienced and skilful general-practitioner obstetricians who gave their assistants a good deal of instruction. I was in general practice for a short time and was admirably taught how to deliver with the forceps by my father-in-law, in whose practice I worked. These skilled men have diminished considerably in numbers, partly because of the increased number of hospital beds and partly because of the larger number of cases taken by midwives. Few practitioners in a city such as Leeds book as many as 30 cases a year. It therefore comes about that a man has much less chance of learning or being taught his obstetrics efficiently in practice than he had 25 years ago. Hence the desire of the Royal College of Obstetricians and Gynaecologists to improve the service by restricting obstetric practice to senior practitioners of experience and those who have had a resident obstetric appointment.

The writer of your leading article appears to take exception to the statement in the *Practitioner* special number that "the average midwife is better trained to deal with normal midwifery than is the average general practitioner." What does he expect? Most midwives in this city book 60 to 80 cases a year, and they spend their whole time in the practice of obstetrics. A few general practitioners may book half these numbers, most of them many less than half. The practitioner, if enthusiastic, may perhaps spend as much as a tenth of his time at obstetrics.

The resident appointment in obstetrics, as in other branches of medicine, can be of great value. It is unfortunate, therefore, that at present few men take one. Usually a man prefers to take an appointment in general medicine or surgery before going into the Forces. For many years now the great majority of our residents have been women, and though it is natural that women should have a special interest in maternity work many of them are soon lost to practice because they marry.

The new graduate in medicine is better trained in obstetrics than his predecessors, but he cannot become skilled unless he has adequate postgraduate experience.—I am, etc.,

Leeds. Andrew M. Claye.

Sir,—Your remarks in your leading article (October 8, p. 799) about the general practitioner's place in the maternity services were long overdue. It is indeed unfortunate that this controversy has engendered a certain amount of resentment on the part of the general practitioner, who feels that the criticisms of his competence are not only unjustified but also unjust, since his own teachers, if not themselves responsible, have at least condoned them.

There must be many general practitioners who until quite recently have had to spend long hours at the bedside taking personal responsibility for normal deliveries assisted only by an untrained handywoman because no midwife was available, and for aught I know there must be many in the remoter parts of the country still doing this. If these doctors have failed to profit by the experience thus gained at the expenditure of so much time and patience it must only be because their teachers have failed to instil into them the fact that every doctor must remain a humble student of medicine until the end of his professional career. It is pertinent to ask where the specialist obtains his experience of normal labour, since, outside the teaching hospitals, most of his normal cases are delivered by his house-surgeons for him. Nor do all house-surgeons

necessarily become specialists, and quite often they go into general practice.

But my purpose, Sir, is not to provide further ammunition for the protagonists in this dispute but to plead that it is not too late to undo the harm that has been done and to try to bring together the specialists, the general practitioners, and the midwives into one team, each complementary to the other and all necessary to the future maternity service. Official policy would seem to be setting out to destroy what vestiges of co-operative spirit remain, and I would humbly suggest that it is ill-advised.

For example, it is the official policy of the hospital boards that in the future the beds under their control in maternity hospitals will be closed to the general-practitioner obstetrician. Surely it would be far better to encourage the general practitioner to deliver primiparae and women with minor types of abnormality in maternity hospitals. It would be an advantage to the patient, whose first pregnancy should be a period of training for future motherhood, to have her baby in proper surroundings, and that her care and training there should be associated with her own general practitioner, for, as you rightly stress, here is the "very root of general practice." It would be an advantage to the specialist to know that those very cases most prone to require his assistance should anything go wrong would be from the first already in an institution suitable for that purpose; this would materially reduce his greatest bugbear, the failed forceps far away in a filthy cottage. It would be an advantage to the midwife, who has to obtain much of her training in such maternity hospitals, to have a ready supply of normal cases for that purpose. And it would be an advantage to the general practitioner himself to know that a select number of his patients can be delivered with all the advantages of modern technique at his disposal.

But above all it would effect an improvement in the whole maternity service, because it would offer a common meeting ground for the keen general practitioner with his colleagues and with the specialists and the midwives with whom he has to work, not only in those casual discussions which inevitably take place in the course of daily visits but in the possibilities for team-work, for regular clinical meetings and discussions, and for staff meetings, and the maternity hospital would thus become a centre for the dissemination of modern teaching and technique.

In due course it would be found that the keenest general-practitioner obstetricians would be anxious to seek opportunities for service in such maternity hospitals, and this would be the means of selecting those who would become most competent and of discouraging the remainder, and thus would bring about the conditions which the Minister of Health is most anxious to encourage. This would be a far more just and equitable method of selecting the best general-practitioner obstetricians than giving this invidious task to a small committee of specialists, who cannot always have the means of assessing the true worth of their more remote colleagues.—I am, etc.,

Wivenhoe, Essex. WALTER RADCLIFFE.

A Year of N.H.S.

SIR,—The review in the *Journal* (October 1, p. 746) of the recently published *Practitioner* dealing with the National Health Service in its first year fails to point out the omission from that journal of any contribution by a worker in the field of preventive and social medicine. The Part III services are referred to only very briefly and incidentally by the medical administrator (undoubtedly a hospital officer) and at somewhat greater length in the paper discussing the Ministry and the Service (almost certainly by a medical officer within that department). This is symptomatic and worthy of note.

It is clear evidence that in the minds of those engaged in Part II and IV services (as represented in this symposium) the Act provides a curative service and not a preventive one. There is no evidence even of the lip service paid in the recent past to social and preventive medicine; there is no reference in the contribution by the young doctors to public health or social medicine as a career—that is significant in itself; no discussion of the difficulties of linking up preventive work with curative work in publicly organized medicine in schools and among young children; no reference to the partial collapse of the school eye service; no reference to the present unsettlement in the public health services; no reference to the absolute exclusion alone among doctors of medical officers of health as such from regional hospital boards.

The obstetrician in his contribution criticizes the general practitioner whom he (collectively) has trained and allowed to graduate, and makes the unpleasant suggestion (unsupported by evidence) that considerations of financial economy have prompted local health authorities to instruct midwives to call in private practitioners early in the pregnancy. A friendly relation between general practitioners and midwives is essential in a world in which specialists are in a small minority, and this is what those local health authorities which are asking midwives to encourage their patients to see their own doctors early in the pregnancy are now trying to secure. The better standard of medical training is, under the General Medical Council, the responsibility of the medical schools with their consultants, and it is a grave responsibility. To improve the obstetric training of both general practitioners and midwives is a better policy and will safeguard the mothers more than by arousing antagonism between them.—I am, etc.,

Dewsbury. E. D. IRVINE.

The Innocence of Deans

SIR,—Dr. E. R. Boland's letter (October 8, p. 812) is rich in entertainment but obscure in intellectual intention. He apparently misinterprets my feelings towards deans, for whom I have the greatest respect. They work hard, and often thanklessly; they have the difficult job of adjusting situations as between crotchety colleagues; they must arrange teaching programmes, deal with difficult students and refractory committees. In a word, theirs is the art of the administrator and of the politician. Unless "honest and faithful subservience to an institution"—the phrase, apparently, so disliked by Dr. Boland—is regarded by them as their first function, they would fail as deans.

But the crux of the whole State medicine problem is the simple question, Is Medicine to be subservient to politics or is it not? The training and general outlook of a dean, or of a "posse," "clutch," or "diabolry" of deans, would incline them to answer yes. Dr. Boland also, I suspect from the possibly not unintentional irrelevance of his letter, would say yes.

One result of the political direction of a previously free profession is this laughable attempt to assess individual professional status on a points system. Lister, James Mackenzie, Ronald Ross, and indeed most pioneers have usually had their contemporary colleagues against them, particularly so their seniors. If the seniors are unsound judges and if the judgment of the juniors is unacceptable, what judiciary, pray, is there left? Well—I forgot the politicians and the good committee men.—I am, etc.,

London, W.1. GEOFFREY BOURNE.

Modern Trends in Radiology

SIR,—Dr. James F. Brailsford in his article entitled "Modern Trends in Radiology" (October 1, p. 724) indicts modern radiology in medical practice. While the charge may itself be accepted, I feel he is less than just when he cites mass radiography as the arch-criminal. Those who practise mass radiography are, on the contrary, less likely to make the omissions he suggests. I will comment on them in his order.

1. No diagnosis is made or suggested to the patient without a clinical examination whether conducted by the director of the unit, the physician to the chest clinic, or the private doctor. The x-ray film is in fact regarded as an integral part of that examination.

2. Mass radiography provides a unique opportunity of studying the normal.

3. Serial radiography with clinical examination is in no way prohibited because a patient first attended a mass miniature radiography unit.

4. It is true that disease may be present before radiological evidence is apparent, but this applies no more to mass radiography of the chest than to other radiography. In fact the problem arises less frequently, as the vast majority of those attending for mass *x* ray consider themselves, or would be considered on clinical examination alone, to be in good health.

5. Those attending mass *x*-ray units are not treated on the *x*-ray appearances alone but on the whole clinical picture.

There is no belief that active progressive disease is symptomless, nor is this concept part of the propaganda. It is found, however, that people with early active and progressive disease often have symptoms so vague and indefinite that it will not occur to them to consult a doctor, but they will nevertheless volunteer for mass radiography.

It is fully realized that a large proportion of persons who have had active pulmonary tuberculosis do in fact recover from it without knowing of its existence, and this fact will doubtless be emphasized when mass radiography has been with us long enough for a useful follow-up of a sufficient number of cases to establish that such recovery is permanent. Does Dr. Brailsford seriously suggest that no patient with active tuberculosis should be acquainted of the fact or treated until his symptoms are sufficiently severe to force him to consult his doctor? Recognition of ill-health can be as elusive to the patient as shadows on an *x* ray are to a radiologist. How frequently one hears a patient say after treatment, "I thought I was well before, but now I realize how much better I am."

I believe mass radiography may in time, by finding cases in a treatable or pre-infective stage, do much to negative the fear and stigma of tuberculosis which has become established in the public mind by the high proportion of advanced and untreatable cases in our midst.—I am, etc.,

London, S.E.12. F. D. BEDDARD.

SIR,—His colleagues in Great Britain know enough about Dr. James F. Brailsford to discount the various extravaganzas in which he indulged in his article entitled "Modern Trends in Radiology" (October 1, p. 724). Dr. Peter Kerley (October 15, p. 870) has drawn attention to some of the grosser misstatements, and I would merely like to draw attention to the absurdity of his recommendation that medical students should perform upon one another "every kind of injection, including ventriculography, myelography, arteriography, etc." This from the director of radiological studies in living anatomy of a distinguished university.

It is disquieting, however, to learn from a footnote that Dr. Brailsford has been talking such nonsense in various parts of the United States. It is important that our American colleagues should realize that these views are Dr. Brailsford's own and do not represent the consensus of intelligent radiological opinion in this country, and it is with that object that I write this letter.—I am, etc.,

London, W.1. S. COCHRANE SHANKS.

Vitamin Deprivation

SIR,—Professor A. C. Frazer (October 1, p. 731) should be congratulated on his conception of a new mechanism in the explanation of vitamin deprivation. The idea of bacterial invasion of the upper small intestine is not novel, and I myself reviewed the literature both for pernicious anaemia[1] and for the sprue syndrome[2] some years ago. Professor Frazer's great merit lies in putting forward the hypothesis that the periodic increase of bacterial invasion into the higher small intestinal regions might result in competition between bacteria and host, leading in many cases to signs of deprivation in the host.

While there are reasons to believe that the deficiency of the vitamin-B group may be connected with interference of absorption in general,[3] Professor Frazer adequately proved that this is not intimately related to the fat-absorption defect in sprue.[3] Many will agree that the competition hypothesis—if this should be proved in the future—might account for the exacerbation of some vitamin deficiencies in general, for selective deficiencies often observed in the sprue syndrome, and also for many other conditions suggested by Professor Frazer. I have, however, some doubts as to the statement that it might explain the administration of one vitamin precipitating the deficiency of another.

The considerable literature dealing with vitamin imbalance contains many well-documented cases where a bacterial invasion of the higher small intestine was most improbable.[4] It has been suggested, when discussing the aetiology of the sprue syndrome, that phosphorylation constitutes an important link between sprue and the B vitamins.[2] It was found later by Magyar that the consumption and excretion of these vitamins were dependent on phosphorylation.[5] The same author reported recently experiments on rats showing that previous administration of a large dose of any of the main members of the vitamin-B group interferes greatly with the absorption of a standard dose of thiamin. He attributes his findings to the exhaustion of the phosphorylating capacity of the animals.[6] Further experiments will have to decide whether this is the real explanation of vitamin imbalance as it is claimed.

This comment is not meant to detract from the importance of the competition hypothesis, and it is hoped that the Birmingham workers will further elaborate this conception.—I am, etc.,

London, W.1. Z. A. LEITNER.

REFERENCES
1 *Haematologica*, 1929, **10**, 15.
2 *Trop. Dis. Bull.*, 1942, **39**, 497.
3 *British Medical Journal*, 1947, **2**, 641.
4 Leitner, Z. A., ibid., 1948, **1**, 917.
5 *Experientia*, 1948, **4**, 33.
6 Magyar, I., and Gabor, G., *Int. Z. Vitaminforsch.*, 1949, **21**, 1.

Infant Vaccination

SIR,—In the current issue of the *Monthly Bulletin of the Ministry of Health* (1949, **8**, 204) Dr. E. T. Conybeare, of the Ministry of Health, gives a report on the amount of infant vaccination in England and Wales during the six months July-December, 1948. He shows that for this period, the first half-year under the new Act, the proportion of infants vaccinated has fallen to about half what it was before the Act came into force. He concludes his article by saying:

"If the figures for 1949, when they become available, show that the decline of infant vaccination under the National Health Service is not temporary, measures, such as an increase in the number of vaccination clinics . . . and the working out of some plan to facilitate domiciliary infant vaccination in areas not served by such clinics, may be urgently required. Such measures, pursued with the energy put into the campaign for immunization against diphtheria, might well produce similar results and make the child population of this country as well vaccinated as that of the United States or other countries, where protection against smallpox is regarded as the important matter that it undoubtedly is."

Is not Dr. Conybeare rather begging a highly debatable question when he makes that final assertion? Is a well-vaccinated child population really such a very important matter in protecting a community such as ours against smallpox? Surely there is a great deal of valid evidence pointing to the opposite conclusion. Decline in infant vaccination is not a new phenomenon. It has been going on continuously for over half a century, but so far from its having been followed by any increase in smallpox mortality the latter has fallen steadily, until now it is practically negligible. Moreover, in those parts of the country where the decline in infant vaccination has been greatest the same decrease in smallpox mortality has been witnessed. Thus in the city of Leicester the average percentage of infants vaccinated has for very many years been under 5 (Dr. Conybeare tells us that it has now fallen to 1.4%), yet during the past 40 years there have been only two deaths from smallpox, and other places have had a similar experience.

After all, it is the adult population who are most exposed to the danger of smallpox, and the effect of infant vaccination in protecting this section of the community is very doubtful. It may reasonably be argued that infant vaccination by masking the disease in adults, when the protection conferred on the individual is wearing off, neutralizes—or more than neutralizes—any value to the community derived from the partial immunity conferred on the individual adult. Incidentally, it may be mentioned that in the 14 years 1932–46 there were in England and Wales only 28 smallpox deaths (an average of two per annum

in a population of 40,000,000), and not one of the fatal cases was under the age of 1 year. Yet in the same period there were 51 deaths from vaccination under 1 year of age.

Dr. Conybeare mentions admiringly the United States and "other countries." What other countries, including U.S.A., can show better results in dealing with smallpox than Great Britain? So I venture to suggest, with all respect to Dr. Conybeare, that perhaps, after all, infant vaccination is not such a very important matter in protecting a community such as ours as he seems to think.—I am, etc.,

Leicester. C. Killick Millard.

Malignant Tertian Malaria

Sir,—In his address on the treatment of malignant tertian malaria Sir Gordon Covell (October 8, p. 773) gives an excellent and comprehensive survey of the present position as regards therapy. In his discussion of diagnosis and symptomatology, however, there is much that many practitioners with long experience of malignant tertian malaria will disagree with. Sir Gordon repeats the warnings about the difficulties of diagnosis—the statement that M.T. malaria may "simulate a great variety of other diseases"—which are to be found in every textbook since Manson's original *Tropical Medicine*. He repeats the classification into cerebral, algid, bilious, remittent, and cardiac forms, which appear to me to be singularly useless and misleading.

Is M.T. malaria really a very difficult disease to diagnose? Does it really imitate other diseases to such an extent? Is it not possible that this view is based on a fundamental fallacy which arose in the early days, when the finding of the recently discovered M.T. parasite in the blood stream of white, black, and brown patients was hailed as the explanation of all their symptoms? Has not a process of disentanglement been in operation over the past quarter-century?

Sir Gordon refers to a series of 80 cases of British soldiers treated by him at Nairobi in the 1914–18 war. They arrived from the Lake Victoria district. All showed M.T. parasites in their blood, but some showed symptoms suggesting dysentery, typhoid, biliary colic, etc. All responded to quinine and hospitalization. I fail to see how this proves the versatility of malarial symptomatology. Surely it is at least possible that some of those troops, under the conditions obtaining, had other diseases besides malaria—bacillary and amoebic dysentery, for instance. Is it not possible that some had double infections of M.T. and quartan? Knowing that area well, I would say it is more than possible.

My own experience in Africa has convinced me that there has been a great deal of nonsense talked about the "protean" nature of M.T. malaria and its so-called pneumonic, dysenteric, appendical, and other "forms." In some thousands of European cases I have treated I have seen a few where malaria was complicated by pneumonia, by dysentery, and by other infections, but I would say that in the main M.T. malaria presents a remarkably constant clinical picture (more so than quartan), besides being quite easy to diagnose in the vast majority of cases. I would say that great harm can be done by teaching young practitioners going to the Tropics that they may have serious difficulty in distinguishing malaria from appendicitis. I have seen only three cases where such difficulty might have arisen. In two of these I removed acutely inflamed appendices in the middle of typical blood-positive malarial attacks. In the third the patient formed an appendical abscess after his malaria had subsided. Nowadays, when I read about appendical forms of malaria, I do what the man in the *Ingoldsby Legends* did: I say no word to indicate a doubt, but . . . Sir Gordon rightly emphasizes the dangers of delay in diagnosis, but his two illustrative cases merely show the effect of *gross* delay and provide two typical histories of untreated M.T. malaria. There was apparently no difficulty in diagnosis, nor were there any extraordinary symptoms. I do not think they should deter anyone from delaying for a short time, unless the case is dangerously ill when first seen or is a young child, in order to establish a microscopical diagnosis. Sir Gordon states that "in a primary case parasites may be so scanty in the peripheral blood during the first few days of fever that they may not be detectable in a blood smear, even if no antimalarial drug has been administered." This is not my experience nor, I am sure, that of many others. If antimalarial drugs are withheld in a patient showing pyrexia, and blood examinations made at intervals over 48 hours, I believe that parasites will be found practically invariably if M.T. malaria is the cause of the pyrexia, and I believe this to be a perfectly safe procedure to adopt. Sir Gordon's method of giving an antimalarial drug after examination of one smear and waiting for the temperature to drop before taking another would tend to confuse rather than clarify diagnosis by making the parasites more difficult to find. Moreover, in a first attack of M.T. malaria the temperature is very unlikely to drop for four to five days even when treated intensively—another very constant feature of this "protean" disease.

In short, I would advise practitioners going to the Tropics not to be too much impressed by classical descriptions of M.T. malaria. (If they do native work they will soon learn not to ascribe a native's pathology to malaria parasites in his blood.) I would advise them to put the greatest reliance on the microscope for diagnosis and not to be put off intelligent use of it for fear of dire calamities, to beware of ascribing atypical symptoms to a disease which follows a very typical course, and to operate on patients who show signs of acute surgical conditions even if there are M.T. parasites in the blood. In modern tropical European practice there is much more harm and confusion caused by ascribing to malaria all manner of symptoms when it does not exist than by failing to recognize it when it does.—I am, etc.,

Craven Arms, Shropshire. P. Ross.

Poliomyelitis

Sir,—Your correspondent, Dr. N. G. Nicholson (October 1, p. 757), describes a series of cases of non-paralytic poliomyelitis occurring in Colombo, and then details his own unfortunate experience. His description of his own symptoms, in particular "the most terrific pain I have ever experienced in my left shoulder" and the delay in appearance of muscle wasting, is quite characteristic of acute brachial radiculitis, or the "shoulder-girdle syndrome."[1 2]

It is interesting to note that Parsonage and Turner[2] describe a case of coincident poliomyelitis and the shoulder-girdle syndrome, and I myself have seen a rather similar case in which the syndrome developed two weeks after an abortive attack of poliomyelitis. The pain in the affected muscles is much more severe in acute brachial radiculitis than I have ever encountered in poliomyelitis.—I am, etc.,

Harrogate. R. Harris.

References

1 Turner, J. W. A., *British Medical Journal*, 1944, **2**, 592.
2 Parsonage, M. J., and Turner, J. W. A., *Lancet*, 1948, **1**, 973.

Poliomyelitis Vaccination

Sir,—Mr. M. H. F. Johnson (October 1, p. 757) has raised an important point in asking why, following the lead of Jenner and Pasteur, active immunization against poliomyelitis is not practised. It has been shown by Kolmer[1] and Brodie[2] that the vaccination of monkeys with living attenuated ricineolated or formalized virus, prepared from the spinal cord of a monkey after serial passage, produced an active immunity sufficient to enable them to withstand intracerebral inoculation of infective doses of virus. These experimental results immediately suggested that a vaccine suitable for human use was feasible.

Field trials with poliomyelitis vaccine have unfortunately been inconclusive, due largely to administrative difficulties. The low morbidity of poliomyelitis (an attack rate of 1 in 1,000 even during epidemics being exceptional) necessitates the immunization of many thousands to show any significant statistical results. Furthermore, it is now accepted that many different strains of poliomyelitis virus exist, some of which show antigenic inter-relationship while others appear antigenically distinct. The experiences of Gillam and Ornstrott[3] and Reynolds and Knox[4] illustrate the difficulties of field trials. These workers together vaccinated 1,000 children, another 1,000 being used as controls. No case of poliomyelitis developed in any of the 2,000 children employed.

The fact that poliomyelitis vaccination is not devoid of serious danger has been shown by Leake,[5] who collected a series of 12 cases; five of the patients died and three of them were left severely paralysed after vaccination. The clinical onset of the disease occurred within 6–14 days of either the first or the second inoculation—i.e., within the accepted incubation

period. Leake, after a careful analysis of all attendant circumstances in these cases, points out: (1) Poliomyelitis was not epidemic in any of the areas where these cases occurred. (2) The expectation of poliomyelitis among the vaccinated, judging by its occurrence by age groups in the community at large, was less than 1/10 of a case in these localities, yet cases occurred. (3) The likelihood of the whole series of cases having occurred by natural causes was extremely small. (4) In none of the cases was exposure to infection outside its own area known to be of any special significance. (5) In every case in which the sequence of events was known, the level of the spinal cord first affected corresponded to the limb in which the injection was made, paralysis beginning either in the same or in the contralateral side. While any one of these cases may have been entirely unconnected with vaccination, the implication as a whole is clear.—I am, etc.,

Manchester. W. P. SWEETNAM.

REFERENCES

1 *Amer. J. med. Sci.*, 1934, **188**, 510.
2 *Science*, 1934, **79**, 594.
3 *Amer. J. publ. Hlth*, 1936, **26**, 113.
4 Ibid., 1936, **26**, 95.
5 *J. Amer. med. Ass.*, 1935, **105**, 2152.

Lead Nipple Shields

SIR,—Shades of Dr. Wansborough! Little did that worthy if imaginary gentleman think when he "invented" his nursery requisite about 50 or 60 years ago that he would cause such apprehension and alarm in 1949. Yet I have no doubt his intentions were kindly and well meant, for these 3-in. (7.5-cm.) disks of thin, smooth metal, carefully shaped to fit the contour of the nipple snugly, like a little conicle-crowned broad-brimmed hat, and with as much zinc as lead in their composition if one may judge from their lightness and shape-retaining qualities, were worn on the nipples between feeding-times and during the night, and removed, of course, when the child was put to the breast.

The Minister of Health reasoned, no doubt correctly, that during the longer periods of rest and warmth the film of milk around the nipple and imprisoned by the shield would turn slightly sour, forming an infinitesimal amount of lead lactate, thus exerting *in situ* a very mild, soothing, and astringent action on the macerated and tender part, akin, as it were, to the same beneficial effect that liq. plumbi subacet. dil. (Goulard's water) has when used as a dressing on moist excoriated surfaces. As regards the risk of lead-poisoning, surely the ordinary instincts of cleanliness would prompt the mother to cleanse the breasts and shields, if not before each feed, at least once or twice daily. However, the Ministry has apparently some startling news for us, and has promised the publication at an early date of the full details of how babies can absorb such an amount of lead by this means as to cause saturnine encephalopathy, a state of poisoning which as a rule, in my experience, indicates a severe saturation with the metal. Let us hope the mothers have not been excreting diachylon taken in the early months of pregnancy.

But apart from the foregoing, who in all the earth prescribes lead nipple shields nowadays? I saw them 40 years ago when in business, and the pair we had then were real museum pieces, marked for many a day as dead stock and quite unsaleable. In this town of 50,000 inhabitants not a single one can be bought. There are 18 chemists—principals and staffs totalling about 100—all handling N.H.A. scripts. Out of these, three had actually seen lead nipple shields many years ago, eight apparently knew about them, and the remainder had never heard of them at all. The same circular from the Ministry has been sent to them too, each one wondering what it is all about.—I am, etc.,

Lancaster. R. G. HOWAT.

SIR,—The announcement in the Press of the Ministry of Health's embargo on the use of lead nipple shields has only just brought to my notice this controversy. Like many women handicapped by severely cracked nipples, I have reason to be grateful for this effective aid to breast-feeding: when all other remedies failed lead nipple shields enabled me to feed each of three babies for a normal period of nine months. If the breasts are thoroughly washed before each feed it is difficult to see how the babies can suffer.

I should like to examine some evidence before I acquiesced in the Ministry's fiat and abandoned the shields for a fourth child, which would inevitably mean weaning at a few days old—in my view a tragedy. I could, with difficulty, obtain a pair of shields from France, where they have been in common use for generations, but such a course of action, in opposition to the full weight of medical opinion in this country, would be a terrifying responsibility for any mother.

Can you tell me where the evidence which led to the Ministry's decision can be examined? And can you perhaps influence the public press to publish the source, so that women can test such evidence against their own experience before making a very difficult decision?—I am, etc.,

Barnstaple, Devon. JOAN S. BLACKSELL.

*** In the *Lancet* of October 8 there is a paper (p. 647) by Dr. I. Gordon and Mr. T. P. Whitehead entitled "Lead Poisoning in an Infant from Lead Nipple Shields" and a letter (p. 674) by Drs. Helen Mackay and Donald Hunter on the dangers of lead nipple shields.—ED., *B.M.J.*

Congenital Pyloric Stenosis

SIR,—The occurrence of congenital pyloric stenosis in three consecutive children in a family is not so unique as Dr. J. L. Adlington (October 1, p. 740) suggests. Brendle[1] records its occurrence in three brothers in the same family, and Fabricius and Vogt-Muller[2] described its occurrence in all four children of the same mother, three of whom had the same father. I saw three consecutive children (two girls and one boy) of the same parents who were successfully treated by "eumydrin" at the Leicester Royal Infirmary. These cases—Nos. 44, 57, and 103—were included in a series of 112 cases of pyloric stenosis admitted over a period of eight years and reported in *Archives of Disease in Childhood* (1947, **22**, 75).—I am, etc.,

Liverpool. R. MCLAREN TODD.

REFERENCES

1 *Mschr. Kinderheilk*, 1937, **68**, 295.
2 *Hospitalstidende*, 1937, **80**, 166.

Symptoms of Psychoneurosis

SIR,—The results of an investigation briefly described below may be of some interest. The symptoms were studied of two groups of medical out-patients and of one group of in-patients on whom the physician's opinion was asked. The 672 patients were seen during Naval service and were mostly men of the Royal Navy and R.A.F. Two-thirds were between 17 and 35 years of age.

A diagnosis of neurosis was made in 31% and 30% of the two out-patient groups and in 24% of the in-patients. When those patients were included whose symptoms were mainly neurotic the percentages were 38, 36, and 34 respectively, with an average of 36% (244 out of 672 patients). Pain was the commonest symptom in these 244 and was complained of by two-thirds of them, often in more than one site. It was a more common symptom in these people than in a sample of non-neurotic patients. In half of those complaining of pain the pain was a headache. One-third of the 244 complained of dyspnoea of some sort (on exertion, on lying down, waking up panting for breath, a feeling that the chest could not be filled, etc.) and one-third complained of insomnia. One-quarter complained of tiredness (weakness, exhaustion) and one-quarter of giddiness ("dizziness"). One-sixth complained of either trembling, palpitations, precordial pain, or abdominal pain. Only about 5% complained of loss of confidence or of loss of concentration or of irritability.

Twenty-two of the 244 patients suffered from a cardiac neurosis. This proportion (9%) is much less than that found among neurotic patients in the Army.[1 2] Fifteen patients may be said to have had a pulmonary neurosis. Fear of tuberculosis appeared to be the commonest cause of this. Eleven had mainly genito-urinary symptoms (enuretic patients without

other evidence of neurosis were not included in the 244). Two patients had a neurosis simulating rheumatism. One-third of the neurotic and mainly neurotic patients gave a family history of psychopathy according to Slater's definition[3] as against 5.9% of the non-neurotic patients.—I am, etc.,

Rochester, Kent. F. A. Richards.

References

[1] Douglas-Wilson, I., *British Medical Journal*, 1944, **1**, 413.
[2] Todd, J. W., ibid., 1944, **1**, 19.
[3] Slater, E. T. O., *J. Neurol. Neurosurg. Psychiat.*, 1943, **6**, 1.

Tetraethylthiuramdisulphide in the Treatment of Alcoholics

Sir,—I was most interested to read Dr. A. E. Carver's article on the treatment of alcoholics with tetraethylthiuramdisulphide (August 27, p. 466). I have used the drug in more than 50 cases of alcoholism during the past eight months, and I fully agree with Dr. Carver's conclusion that it is a useful ancillary in the treatment of this serious and troublesome illness.

Dr. Carver describes two methods of the administration of the drug—either to give it surreptitiously without the patient's knowledge or consent, or to give it after a full explanation with the patient's co-operation. I consider that the first method he describes is dangerous. I have observed a few very severe reactions following the ingestion of alcohol in sensitized patients which, if they had occurred in the patient's own home or in public, might have led to serious consequences.

On a recent visit to Scandinavian hospitals, where the drug is widely used, several deaths following the treatment were reported to me. Jones[1] has reported very fully the case of a healthy young male who died a few hours after taking a test dose of an ounce of rum, following premedication with tetraethylthiuramdisulphide during the previous four days. It is clear, therefore, that this is potentially a dangerous drug unless its administration is carefully controlled.

The patient's reaction to alcohol when taking the drug should not be left to chance, but a test should be carried out under hospital conditions. It is wise, too, to inform the patient and his relatives that alarming symptoms may follow the ingestion of alcohol, and that a clinical trial with a small amount of alcohol will be made to test out his reactions before he is allowed to run the risk of drinking at his own discretion. Unless these precautions are taken I feel there is a danger that this valuable adjunct to the treatment of alcoholism will fall into disrepute.

I am surprised at Dr. Carver's suggestion that the drug should be given only for a month or two. It is surely a matter of clinical experience that an alcoholic must be considered prone to relapse until he has been abstinent for a very much longer period.—I am, etc.,

Dublin. J. N. P. Moore.

Reference

[1] *Canad. med. Ass. J.*, 1949, **60**, 609.

Treatment of Varicose Veins

Sir,—Mr. C. H. Wickham Lawes has misread and misquoted me; and, moreover, his otherwise courteous letter (September 24, p. 708) has given no less provocation by his repeated "of course"—a term that I hope you will allow me to show fits too loosely to his arguments about a matter of some importance. He has "tried most methods including Dr. Hanschell's (it is, of course, not new)." In my letter (March 19, p. 500) I gave a summary of this method, brief yet sufficiently precise to be intelligible and identifiable. It is not new, in so far as I arrived at it very slowly over a period of years by trial and error and comparison with controls; have practised it for a decade; and find it adopted by colleagues. It is new only in that no one else has yet described it (nor have I, fully, in boring detail). I take leave, therefore, with due respect to Mr. Lawes, to doubt whether he knew of it, "of course," or anyhow, or has in fact tried it; and I beg him to extend his courtesy to re-read my letter with closer attention.

Again, "Dr. Hanschell states" that minimal injections give extra pain and longer convalescence, and that sclerosant injection is a dangerous ally and a useless one. Of these statements Mr. Lawes writes, "Of course they are far from correct." But, Sir, what I wrote was to the effect that he would find his minimal injections, as ally to ligations, had served only to give a pain and convalescence respectively extra and longer than that attached to ligations alone in control legs. How correct that is, Mr. Lawes can know "of course" only if he (as I had) tried those controls—and he hasn't. I wrote that sclerosant injection was dangerous *or* useless, not *and* useless. The difference in a serious discussion is not unimportant. Will not Mr. Lawes oblige by re-reading my letter? Furthermore, he states, "Operation or injection alone is not enough." Which certainly confesses that the uselessness of injection alone is not "of course far from correct."

Now it has happened that some (however few) deaths have resulted from "the method of choice . . . a combination of operation and injection." I suggest it is not "of course far from correct" to find here a not dubious implication that some injection, although not enough alone, may be dangerous enough as an ally to operation—and the plain corollary that this ally injection to be safe must be useless. I have no doubt that Mr. Lawes will have more than glanced at Sir Heneage Ogilvie's restrained damning (September 24, p. 665), on the facts of observation (and how timely), of this ally injection. I have given facts of observation, that any one may find for himself, to speak for themselves. "My opinion" would be supererogatory pomp, uncomplimentary to a professional brother and unbecoming to me. It would be, of course, far from correct to pretend that a death here and there, following this or that induction of thrombophlebitis, made a holocaust: but it has made more than one dead human, who would not have died of varicose veins.—I am, etc.,

London, W.1. H. M. Hanschell.

Serous Fluid in Wounds

Sir,—After certain operations it is common to find an accumulation of serous fluid in the wound. This is usually of minor degree, but on occasion the effusion may be gross, persistent, and have the characters of a lymphatic fistula. Such is occasionally the case after a radical mastectomy, after dissections of the lymphatics of the lower neck, and after dissections of lymphatics in the groin and upper thigh. If the leakage does not cease spontaneously or respond to simple measures such as firm strapping, the condition appears readily curable by the injection of one of the sclerosants used for the treatment of varicose veins.

Exploration of such wounds shows, after about 10 days, a cavity lined with granulation tissue. No doubt there is by this time a very definite walling-off by the granulation-tissue barrier and fibrosis deep to it. The method used would therefore appear safe, providing the wound is not clinically septic. Apart from its use after mastectomy and similar operations I have used it with success in a case of pancreatic fistula. As illustrating the method, the following case may be quoted.

An elderly woman, two weeks after radical mastectomy, was having over 600 ml. of serous fluid removed from the wound, by probing and pressure, each day. The skin wound was well healed and the evacuated fluid not purulent. A rubber catheter was introduced into the cavity as far as it would go and all the fluid evacuated. Monoethanolamine oleate solution (15 ml.) was then injected via the catheter, the catheter removed, and the chest wall firmly bandaged. Twelve hours later the patient complained of some burning pain. A catheter was inserted and the cavity irrigated with normal saline, stringy clots of exudate being thus removed, along with, presumably, surplus sclerosant. A firm dressing was applied for 48 hours. There was no further discomfort, no visible reaction, and no further accumulation of fluid. The patient was discharged a few days later.

Both monoethanolamine oleate and "ethamolin" have been used. The amount required varies with the size of the cavity—from 5 to 15 ml. It is seldom necessary to repeat the treatment. The above case is the only one in which irrigation to remove surplus sclerosant and debris has been necessary—if indeed it was.

It would appear that the treatment acts in two ways: first, by the coagulation of albuminous fluid a stringy tenacious jelly is produced which glues the walls of the cavity together and occludes open lymphatic channels; secondly, the irritation of

the cavity walls enhances the effect and probably aids adherence of the gel. No general or regional reaction has been observed. The number of cases treated has been small, and one feels that the treatment should be used with care and discrimination. The method has proved most satisfactory in my experience. I do not imagine it to be at all original, but as I have not seen it recorded it seems a pity not to make it more widely known.—I am, etc.,

Dartford Kent. STEPHEN BARCLAY.

Streptomycin in General Practice

SIR,—It is very pleasing that the production of streptomycin has so increased that the supply and distribution of the drug no longer require to be organized by the Ministry of Health through various "key" hospitals. Under new regulations coming into force in November streptomycin will be available to all on prescription. It has, however, been the experience locally, and no doubt the same has been the case elsewhere, that in recent months there has been no difficulty in obtaining adequate, prompt supplies of streptomycin for all those cases of tuberculosis encountered at the chest clinic and in hospital who may be expected, in the light of present knowledge, to be benefited by the treatment.

In view of the prolonged course of many forms of tuberculosis and the fact that cases of advanced or chronic phthisis may have to wait nearly a year for hospital treatment, or may never be admitted to an institution because of the shortage of beds, it seems likely to me that many general practitioners will be moved by the laudable desire to do something for their patients to prescribe streptomycin in cases not really suitable. Where general practitioners hesitate, some may be pushed into this course by anxious patients who have heard of the wonder-working medicine.

Apart from possible toxic effects, a very great danger exists in the frequent development of resistance to streptomycin in the tubercle bacilli. If chronic pulmonary cases are given prolonged courses we may find that without benefiting the patients we have produced chronic carriers of streptomycin-resistant bacilli. Any new patients infected by them with these bacilli, and as a result suffering from miliary, meningeal, or other forms of tuberculosis previously responsive to streptomycin, will be unable to be helped. They will have to get better without the help of streptomycin. The meningeal cases will die, and the chest cases will further spread the resistant bacilli. In short, we shall be back where we were five years ago.

It is significant that in the official notice published in the *Journal* of October 1 (p. 752) it was found necessary to give advice on the proper use of streptomycin. I feel, however, that it is too much to expect of general practitioners that they will entirely refrain from using streptomycin in those cases of chronic or advanced disease which form the majority of the tuberculous patients whom they have to treat at home.

I would suggest, therefore, that it would be better for all that the use of streptomycin should depend upon a hospital physician's prescription, just as have been, I understand, less potentially dangerous remedies such as surgical trusses for herniae and physiotherapeutic measures. I hope the responsible bodies will act in this matter.—I am, etc.,

Welwyn Garden City, Herts. B. COUTS.

POINTS FROM LETTERS

Transitory Retrobulbar Neuritis

Dr. HORATIO MATTHEWS (London, W.13) writes: Your critic (September 17, p. 662) is a bit too severe. In my 40 years of eye work I have on several occasions come across transient depreciation of visual acuity following local sepsis. In one case the patient was a G.P. whose visual acuity fell in the right eye from 6/6 to 6/9 with obvious embarrassment within a week of removal of a meibomian cyst from that eye. And there are many I could recall associated with sinus infections. I do hope too much emphasis will not be laid on hysteria. The diagnosis of ? mild or axial or macular retrobulbar neuritis is involved anyway. Is it possible that the whole business is not retrobulbar (in most instances) but microscopically macular ?

Obituary

JAMES KYLE, M.R.C.S., L.R.C.P.

Air Commodore James Kyle, for the past four years assistant director of medical services of the British Overseas Airways Corporation, died suddenly in St. George's Hospital on October 8. He was born in 1888, and was educated first at Watson's College, Edinburgh, and later at Shrewsbury. He studied medicine at Guy's Hospital before the first world war, but left his medical studies in 1914 to serve as a combatant in the Artists' Rifles. He was gassed in France and returned to his medical school at the end of 1916, taking the Conjoint diploma in 1918. After qualifying he was for a short time an assistant medical officer at Lambeth Hospital. In the Royal Air Force, in which he served as a regular officer from 1919 to 1945, he held many important posts.

Sir Harold Whittingham writes: "Jimmy," as he was known in the Royal Air Force and among his wide circle of friends, was commandant of the Medical Training Establishment and Depot just before the war and during most of the war period. Here he was to a large extent responsible for the high ideals instilled into the R.A.F. medical officers and medical orderlies which did so much to mould their characters and to build up a medical service which won great distinction during the recent war.

Kyle had natural charm and grace, and was good-humoured, kind-hearted and generous, possessed of much common sense and a breadth of mind that always appreciated and gave due consideration to the other person's point of view. He was calm, tactful, and outstandingly loyal, and was an ideal administrator beloved and respected by his colleagues, staff, students, and all who had to deal with him. Some eleven years ago he had a severe attack of coronary occlusion. Despite this he bravely and unflinchingly carried on onerous duties in the Service throughout the war and, after his retirement from the Royal Air Force, in the medical service of the British Overseas Airways Corporation, playing a prominent part in its establishment and administration. In addition he undertook the duties of R.A.F. representative on the Armed Forces Committee and on the Council of the British Medical Association. In this committee and at all times he worked hard to improve the conditions of the medical service of the Royal Air Force, which he loved so well. Those of us who have been privileged to serve alongside him for the past thirty years cannot speak too highly of his contribution to Service and aviation medicine, nor of the value of his friendship, help, and advice. We wish to express our deepest sympathy with his wife and two daughters in their great loss.

Dr. JAMES MCALISTER RAMSAY died in an Edinburgh nursing-home on July 26 at the age of 79. He was born in Airdrie, Lanarkshire. It was originally intended that he should be a schoolmaster, and he did some teaching, but his heart was in medicine. He obtained the triple qualification of Edinburgh and Glasgow in 1896, and after preliminary assistantships in Sheffield and Glasgow he took up practice at Parkhead in Glasgow. He built up a successful practice and continued his work there until 1914, when he was appointed medical officer to the Fife office of the Mineowners Defence and Mutual Insurance Association, Ltd. In the exercise of this office he came in contact with most of the doctors practising in the mining areas in Fife and earned their respect and esteem. He was a popular examiner for the St. Andrews Ambulance Association, having the knack of putting candidates at their ease and drawing the best out of them. He was made a J.P. in 1930,

Dr. Ramsay retired in 1945 and came to live in Limekilns, a village outside Dunfermline, where he took part in all the social activities of the village and formed a new circle of friends. He kept his hand in professionally by occasionally deputizing for the local doctor, and he was always ready to give of his best in any emergency. He was a cultured, genial, and kindly man, and his passing is regretted by all who knew him.—R. C. W.

Dr. John Pridmore Raban died in Bristol on October 2 at the early age of 44. Born at Harpenden, Hertfordshire, he received his medical education at the Middlesex Hospital, taking the Conjoint diploma in 1929. After an appointment as house-physician at St. James's Hospital, Balham, he returned to the Middlesex, where he became in turn house-surgeon to Sir Gordon Gordon-Taylor, to the ear, nose, and throat department, and to the gynaecological and midwifery department. It was then that he decided to make radiotherapy his specialty, and he was appointed to what has since become the Meyerstein Institute of Radiotherapy. He took at this time the D.M.R.E., and continued to gain experience until the outbreak of war. In his student days John Raban had been a keen member of the University of London O.T.C., and on qualifying he took a commission in the R.A.M.C. (T.A.), assuming command of the company composed of cadets from the Middlesex and St. Mary's. The training and seniority so gained stood him in good stead during the war years. After a period as radiologist to a general hospital in India, he was given command of one of the first two units of its kind—a Forward Malarial Treatment Unit. Following inevitable teething troubles, this unit moved into the Burmese jungle, where its operational success was outstanding, and recognition of this was accorded by John Raban's mention in dispatches. His final war appointment was to the command, as full colonel, of a general hospital in Ceylon. In 1945 he returned to the Middlesex as first assistant in the Meyerstein Institute, and subsequently was appointed radiotherapist to the Bristol Royal Hospital. With the change of administration in July, 1948, his sphere became that of the United Bristol Hospitals. It was soon after his return to civilian life that his health began to fail, and there can be no greater testimony to his courage and tenacity of purpose than the success he made of this responsible task against increasing odds. He stuck to his job until a few days before his death. John, as he was affectionately known to all colleagues from the most senior to the most junior, never made any claim to academic brilliance. But this was more than offset by a fund of common sense, of human understanding, and an ever-growing clinical intuition. His judgment was respected by all. His was a strong character which enabled him in all circumstances to speak his mind, and was shown perhaps best in his great qualities of leadership. In both war and peace he earned the respect, loyalty, and friendship of all those who served under him. He was blessed with a great sense of humour, and he loved gaiety. These latter qualities were shown in a most successful series of amateur revues which he produced and took part in during his earlier days. He also enjoyed his sport, being a keen horseman and playing for his hospital at rugger. Those who knew him will feel the world a poorer place for his departure. He leaves a widow.—L. C. B.

Dr. S. Curwen writes: I shall always remember John Raban for his great quality of trying to make life as easy as possible for others. A more selfish man could well have preserved himself, but John, with that apologetic way of his, was always so anxious to pull his full weight that he wore himself out.

Dr. Kenrick Stanton Wise, whose death was announced over a year ago, was Surgeon-General in British Guiana from 1914 to 1919, and in Trinidad and Tobago from 1919 to 1936.

A former colleague of his, Dr. J. E. A. Boucand, writes: Dr. Wise arrived in Trinidad just in time to introduce fundamental changes aimed at improving the efficiency of the health services. His was the task of putting into effect the Public Health Ordinance of 1915. Also in 1919 he was appointed chairman of a local committee to inquire into the organization of the medical service. The main recommendations of this committee provided for increases in personnel and in the salaries of medical officers and nurses. As a result of further requests for an improved service, in 1932 another committee with Dr. Wise as chairman was appointed. The report of this committee showed evidence of a very searching inquiry and contained recommendations affecting all branches of the health service. Dr. Wise resigned from the Service in 1936, and was therefore unable to witness the implementation of these recommendations. During his long term of office lepers were transferred from the mainland to a settlement on an island, Chacachacare, where the inmates benefited from the most modern advances in the treatment of leprosy, and their life was made generally more agreeable. The domiciliary treatment of non-infectious cases was encouraged. Dr. Wise was responsible for the setting up of a new "House of Refuge," a modern institution for the treatment and care of the aged and destitute. He urged with success the provision of facilities for postgraduate study, improved the training of nurses, and stressed the need for residential accommodation for nurses. He made great efforts to have a sanatorium established, and formulated the first plans for renovating and extending the Colonial Hospital, Port of Spain, and for rebuilding the Colonial Hospital at San Fernando. He introduced the ear, nose, and throat clinic, the eye clinic, the dental clinic, and a venereal diseases clinic, and was a strong advocate of the medical inspection of schools and of intensification of antimalarial work. He was an able pathologist and born administrator, realistic in his outlook. He was a quiet thinker, with a ready grasp of the most difficult problem. He did much for the West Indian doctors and nurses, but failed in his endeavour to establish a school of dispensing in Trinidad. A man of decision, with a great respect for the opinion of others, he had a fine understanding of human nature, and was able to assess at their true values the officers in his department. Dr. Wise lived a quiet life in the Colony, retreating every week-end to his country seat at Morne Bleu. He spent his leisure moments in the study of history, and was the founder of the Trinidad Historical Society and its first president. His ability and public service were recognized by his appointment to the Executive Council of the Colony. Great regret and sorrow were felt when news of his death in London belatedly reached the Colony he served so well and where he left so many lasting memories.

Medico-Legal

OVERDOSE OF NITROUS OXIDE

[From Our Medico-Legal Correspondent]

A married woman of 38 underwent a minor operation on a septic thumb at the Adelaide Hospital, Dublin, under nitrous oxide and oxygen anaesthesia. The oxygen cylinder was empty, and the student nurse who was assisting was sent for another. She brought from the rack outside the door of the theatre a cylinder which contained, not oxygen, but nitrous oxide. After a few minutes the woman house-surgeon who gave the anaesthetic noticed that the patient was slightly blue and turned off the cylinder which she knew to contain nitrous oxide, but left turned on the new one, which she in error thought to contain oxygen. It was then discovered that this, too, was a nitrous-oxide cylinder. The mask was removed and artificial respiration was continued for two hours, but the patient did not recover consciousness. An account of the inquest[1] on May 31 appeared in this section of the *Journal*.

The prosecuting authorities summoned the house-surgeon[2] before the Dublin District Court on a charge of manslaughter. The student nurse said in evidence that she had been in training for two years but had never previously assisted in the minor operating theatre when a general anaesthetic was being administered. There was no qualified nurse in the theatre at the time. She did not then know of the distinguishing marks on both types of cylinders. She had thought that the cylinders in the rack, about four, were all oxygen cylinders, and had not looked

[1] *British Medical Journal*, August 27, p. 490.
[2] *Irish Times*, September 2, 6, 9, and 20.

at the one she brought into the theatre. A statement made by the house-surgeon showed that she thought the cylinder brought by the nurse contained oxygen, but she did not check it. Other evidence showed that oxygen cylinders used in the minor theatre were black with a white top and were stencilled "O_2" on the neck. Nitrous-oxide cylinders were plain black with a green label bearing the words "nitrous oxide," and both the cylinders in the machine had such a label, though they were not produced in court. Labels and paint were not always in good condition, but the manufacturers repainted the cylinders at least every two years, and often much more frequently. Each type had a differently coloured label and a different serial number. The fittings and valves were identical; in the appliance used in the present case the cylinders were clamped and not screwed into position.

Giving judgment, District Justice Mangan refused to commit the doctor for trial. He found that there had been a default by the doctor, but that the State had not proved that the death had been due to that default. The patient's recent confinement might, as the medical evidence had suggested, have had the effect of raising her blood pressure under the anaesthetic and of leading to a cerebral haemorrhage. The State had not brought evidence of the cause of death, nor even shown that a necropsy had been performed.

Comment

The very full reports in the Irish press do not give any answer to the question why the prosecuting authorities saw fit to arraign this young doctor on a charge of manslaughter. The textbooks show that a much greater degree of negligence is necessary to support a criminal charge than to justify an award of damages in a civil action. The conduct must show such disregard for the life and safety of another as to amount to a crime and deserve punishment. There is no indication in the report that the State adduced any evidence of negligence beyond the mere fact that the accident had occurred, nor was the degree of negligence material to the judgment of acquittal. The prosecutor's omission to lay the groundwork of the case was sufficient to secure that fortunate result. But it is a melancholy reflection that such accidents can still happen after all the fatalities that have already been due to this cause and all the work that the Association of Anaesthetists, the Medical Defence Union, and other bodies have done to prevent them.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

A course of lectures, primarily intended for general practitioners, began on October 12, when Dr. A. M. McFarlan spoke on "Preventing Epidemics: the Doctor's Role." Further lectures in the series, which has been arranged by Professor A. Leslie Banks, Professor of Human Ecology in the University, will be given on the second Wednesday of each month from November, 1949, to July, 1950, at 2.30 p.m., at Addenbrooke's Hospital, Cambridge. Details will be published in the "Societies and Lectures" column of the *Journal*.

UNIVERSITY OF DURHAM

Dr. Arthur Hughes will deliver the sixth Rutherford Morison Lecture on "The Study of the Living Cell" at the Royal Victoria Infirmary, Newcastle-upon-Tyne, on Thursday, November 17, at 5.15 p.m.

UNIVERSITY OF LONDON

Erwin Stengel, M.D., has been appointed to the University Readership in Psychiatry tenable at the Institute of Psychiatry, from October 1.

UNIVERSITY OF WALES

The following candidates for the degrees of M.B., B.Ch. at the Welsh National School of Medicine have satisfied the examiners at the examination indicated:

Hygiene.—A. G. Alexander, D. F. Brown, Josephine J. Candy, D. E. Copas, B. M. Davies, Ilid M. L. Davies, S. I. Davies, J. M. S. Dixon, J. L. A. Dowse, D. R. T. Evans, J. Evans, B. M. Frost Smith, B. J. Fudge, S. G. Gang, Nansi G. Gwynne, A. R. Harris, A. J. Hooper, Dilwyn T. Jones, Mary E. V. Jones, J. Magell, T. M. Morgan, W. B. Morgan, E. D. Morris, T. L. Morris, G. J. Moses, Margaret Pugh, Dilys Rees, T. A. I. Rees, T. B. Stephens, A. P. Thomas, Margaret E. Thomas, Margaret H. J. Thomas, Anne G. Tighe.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a quarterly meeting of the Council of the College, held on October 13, with the President, Sir Cecil Wakeley, in the chair, a resolution of condolence was passed on the death of Mr. Robert Milne, a past-member of the Court of Examiners.

It was reported that Professor R. V. Bradlaw would deliver the first Webb-Johnson Lecture and that Dr. John Gillies would be the Joseph Clover Lecturer for 1950.

A Diploma of Fellowship was granted to E. J. P. Dennehy.

Diplomas of Membership were granted to R. T. Hughes and O. L. Thomas.

Other diplomas were granted as follows:

Fellowship in Dental Surgery.—S. Wilson Charles, R. Fairhurst, G. W. Cathergood, A. R. Thompson, W. F. Collyer, K. P. Liddelow, A. T. Marston, J. W. E. Snawdon, A. M. Norsnell.

Fellowship of the Faculty of Anaesthetists.—N. Macdonald, T. Macdonald, R. A. Hingson (Baltimore, U.S.A.), Harry Daly (Sydney, New South Wales).

Diplomas in Tropical Medicine and Hygiene, in Ophthalmic Medicine and Surgery, in Industrial Health, in Child Health, and in Physical Medicine were granted jointly with the Royal College of Physicians of London to the following successful candidates:

Diploma in Tropical Medicine and Hygiene.—M. el H. Abu Bakr, I. F. Bache, D. N. Banerjee, D. Banerjee, P. H. Birks, S. M. H. Bokhari, S. Chen, Gladys Connor, J. M. Daniel, K. K. Datey, M. M. Desai, J. C. Dutta, H. El Hakim, S. Fazlullah, A. C. Franks, F. C. Harris, J. M. Karim Rehmany, P. W. Kent, S. M. A. Khadri, H. K. Kong, W. S. Kulesza, D. Lawrence, T. Lee, W. S. M. Ling, I. A. McGregor, D. S. McLaren, H. G. McQuade, K. R. Mahajan, A. H. Marsh, A. N. I. Meneces, Deirdre Moore, J. M. Mungavin, C. K. Newman, Gwynfryn A. Owen, W. R. Rochester, A. M. A. Shamy, A. Singh, R. P. Sinha, I. M. S. Stewart, D. E. Thompson, I. G. Thomson, F. G. Williams.

Diploma in Ophthalmic Medicine and Surgery.—M. M. Ahmad, A. A. Al-Hassany, P. E. Anderson, E. L. Arnold, P. W. Arundell, L. G. Bell, A. Bhattacharya, L. S. Bhave, B. J. Campbell, F. W. Campbell, R. L. Dudhia, G. Forrester, E. Gartside, C. Goldin, J. S. Gourlay, H. J. Harcourt, M. M. Hasan, R. J. A. Heron, R. M. Hewat, K. A. Jabbar, D. B. Jagger, Ruby E. Joseph, W. F. Kinnear, K. Lahiri, S. T. Leong, F.-M. Li, Ethel M. J. Loudon, J. D. McConn, D. G. S. MacPherson, W. G. Merriman, S. S. F. Munro, A. H. O'Malley, R. E. O'Neal, J. V. O'Sullivan, V. Raghavachar, S. R. Robson, S. V. Rush, A. N. Sabbagh, O. W. Salkeld, A. C. Sandston, J. W. R. Sarkies, A. G. Shane, B. S. Sher, G. F. G. Siggins, P. Sivasubramaniam, Marjory B. Snodgrass, M. J. Squires, A. Stafford Steen, A. V. Stevens, K. Vythilingham, A. G. Zalzala.

Diploma in Industrial Health.—L. Banerji, J. J. A. Blakely, C. Crowley, J. J. Das, C. D. Edwards, P. J. Feeny, C. J. Goedvolk, J. Gregory, G. G. Mathews, P. A. B. Raffle, S. K. Raychaudhuri, J. B. L. Tombleson, R. N. E. Watt.

Diploma in Child Health.—C. Abraham, Patience C. Agate, Edith M. M. Alexander, S. U.-D. M. Anabtawi, N. P. Bector, N. R. Butler, W. L. Calnan, J. D. Chalmers, B. E. Cohen, V. B. B. Conaglen, E. G. Cook, Rosemary I. Cook, Jessica B. Core, Flora C. Cowan, J. O. Craig, B. N. Das Gupta, Gwendoline A. M. Donald, W. Edgar, G. V. Feldman, P. M. S. Fischer, Joan Frankton, Patricia Frodsham, W. M. Fyfe, J. M. Garvie, Dora Green, L. Haas, D. C. Henchman, Elisabeth C. W. James, K. E. Jefferson, Barbara Jennings, A. Jervis, A. C. Kendall, Sibyl D. Kiani, G. V. Kinariwala, Grace R. B. Kumarakulasinghe, B. Lake, N. H. Low, R. McDonald, Elizabeth M. Mackie, R. L. Macpherson, Mary R. Menzies, E. H. Minors, E. H. Mirando, M. Mirchandani, Jean Mitchell, Cecil M. Moore, Janet H. Mountford, D. N. Mukherjee, Annie M. Peach, I. C. Peebles, A. F. S. Perera, Maeve Powell, Phyllis Rashbass, Helena M. Reckless, R. V. Rele, Stella M. Ring, E. G. G. Roberts, Marion C. Robinson, A. A. W. Roe, Sheila MacL. Ross, C. M. H. Rotman, R. D. Rowe, R. C. Roxburgh, M. H. Russell, T. R. Savage, Isabel B. Schooling, N. L. Sharma, Margot Shiner, Joan E. T. Spong, J. Steven, A. F. H. Stewart, Victoria W. Symonds, J. J. Tillie, W. M. L. Turner, B. P. Webber, O. H. Wolff, S. Wolff, F. B. M. Woodhouse.

Diploma in Physical Medicine.—A. R. Brown, W. A. Fell, R. Harris, Ursula E. K. Leitner, A. T. Richardson, B. Shanson, G. R. M. Sutcliffe, J. M. Titcombe, N. M. Vallely.

The following hospitals were recognized under the Fellowship regulations in respect of the resident surgical post required of candidates for the Final Fellowship examination: Amersham General Hospital (resident surgical officer and house-surgeon); Stepping Hill Hospital, Stockport (resident surgical officer and resident assistant surgical officer).

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended October 1. [No. 39

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each Infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1949					1948 (Corresponding Week)				
	(a)	(b)	(c)	(d)	(e)	(a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	25	3	14	1	—	28	2	26	2	2
Deaths		1	—				3	—		
Diphtheria	76	8	21	2	7	114	15	55	10	2
Deaths	1	—	—	—	—	1	—	—	—	—
Dysentery	163	24	68	1	6	58	12	59	1	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	1	—	—	—	—	1	—	—	—	—
Deaths		1					—			
Erysipelas			22	3	2			26	12	7
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				120					57	
Deaths	34	3	8	7	6	29	3	5	3	2
Measles*	780	40	27	51	45	3,546	94	67	45	71
Deaths†			—	—	—			—	—	—
Ophthalmia neonatorum	39	5	6	—	—	65	6	20	1	—
Deaths										
Paratyphoid fever	24	1	1(A) 10(B)	3(B)	1(B)	6	—	2(B)	3(B)	2(B)
Deaths	1	—	—	—	—	—	—	—	—	—
Pneumonia, influenzal	313	16	1	3	2	402	22	2	1	—
Deaths (from influenza)‡	4	—	—	—	1	5	—	—	—	—
Pneumonia, primary			139	15				171	26	
Deaths	94	15		5	7	150	21		6	7
Polio-encephalitis, acute	26	—				5	2			
Deaths										
Poliomyelitis, acute	331	44	7	—	1	83	7	6	1	1
Deaths§	23	4				2	1			
Puerperal fever		—	8				—	13		—
Deaths										
Puerperal pyrexia‖	104	8	7	—	5	97	5	10	2	—
Deaths		—					—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,305	112	204	96	104	1,234	79	249	126	51
Deaths†			—	—	—			—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever	12	4	1	2	—	40	1	—	2	—
Deaths	—	—	—	—	—	1	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	956	43	52	66	65	2,204	157	69	44	24
Deaths	2	—	1	1	2	5	1	—	1	1
Deaths (0–1 year)	230	27	41	27	16	255	40	39	19	14
Deaths (excluding stillbirths)	3,972	602	524	166	107	4,239	663	527	168	109
Annual death rate (per 1,000 persons living)			10·5	10·3				10·6	10·5	
Live births	7,738	1213	899	347	236	8,066	1269	979	473	242
Annual rate per 1,000 persons living			18·0	21·5				19·8	29·6	
Stillbirths	184	25	20			189	22	36		
Rate per 1,000 total births (including stillborn)			22					35		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined.

‖ Includes puerperal fever for England and Wales and Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications in *England and Wales* for the week ended October 8 were: poliomyelitis 340 (331), polio-encephalitis 34 (26). The figures for the previous week are shown in parentheses. The high prevalence this year is being prolonged beyond the usual time.

The following counties reported multiple cases (poliomyelitis and polio-encephalitis together): London 52 (44), Bedford 5 (5), Berkshire 6 (5), Buckingham 2 (2), Cambridge 3 (0), Chester 5 (4), Cornwall 2 (8), Devon 3 (1), Dorset 7 (5), Durham 2 (3), Essex 31 (26), Gloucester 23 (17), Hertford 4 (12), Kent 26 (19), Lancaster 24 (41), Leicester 4 (2), Lincolnshire, Lindsey 6 (8), Middlesex 30 (18), Norfolk 4 (4), Northampton 4 (4), Northumberland 6 (0), Nottingham 8 (9), Salop 2 (0), Somerset 6 (6), Southampton 4 (7), Suffolk East 4 (2), Surrey 9 (9), Sussex East 2 (5), Warwick 19 (13), Westmorland 2 (0), Wiltshire 4 (8), Yorks East Riding 2 (3), Yorks North Riding 3 (2), Yorks West Riding 50 (38), Glamorgan 7 (6).

Discussion of Table

In *England and Wales* there were increases in the notifications of scarlet fever 208, measles 121, acute pneumonia 87, dysentery 85, and poliomyelitis 63. The only decreases were in the incidence of whooping-cough 105 and diphtheria 16.

The largest increase in the incidence of scarlet fever was 47 in Lancashire. A small increase in the notifications of measles was recorded in most areas; in the north-western counties, however, a fall of 27 was reported.

The largest falls in the notifications of whooping-cough were Warwickshire 39, Yorkshire West Riding 37, and Lancashire 31. A rise was recorded in the incidence of pneumonia in every region except in the south-eastern and south-western counties.

The large rise in the incidence of dysentery was contributed by Lancashire, where 102 cases were notified (Ince in Makerfield U.D. 53, Liverpool C.B. 15, Abram U.D. 10). In London the notifications of dysentery rose from 16 to 24 (Hampstead 18). There was a large incidence of food-poisoning in Lancashire 270 (Liverpool C.B. 257); London 92 (St. Marylebone 67); and Essex 55 (Southend-on-Sea C.B. 20).

In *Scotland* increases were recorded in the notifications of scarlet fever 39 and of acute primary pneumonia 21. The rise in the incidence of scarlet fever occurred in the eastern and western areas. A decrease of 10 in the notifications of dysentery was recorded in Glasgow. An outbreak of paratyphoid B affecting 9 persons was notified in Lanark county.

In *Eire* there were increases in the notifications of scarlet fever 23, whooping-cough 23, and measles 26, with a decrease of 16 in the incidence of diarrhoea and enteritis. The rise in the notifications of measles was due to an outbreak of 24 cases in Waterford C.B.

In *Northern Ireland* an increased incidence was reported for whooping-cough 31, scarlet fever 9, and measles 15. The largest increases were: whooping-cough, Belfast C.B. 20; measles, Co. Down 20; scarlet fever, Belfast C.B. 9.

German Statistics

The *Monthly Statistical Bulletin of the Control Commission for Germany (British Element)* is to be discontinued in its present form. The last issue was that for July, which has just been published. Most of its contents will be continued in *Wirtschaft und Statistik* (published by Kohlhammer Verlag, Stuttgart. The articles and reports will be in German only, but a glossary will be appended giving translations into English of table headings, important footnotes, and explanations.

Diphtheria in Scotland

According to an analysis in the October *Health Bulletin* issued by the Department of Health for Scotland, confirmed cases of diphtheria in 1948 numbered 723, and of these 521 occurred in persons who had not been immunized. Deaths in Scotland in 1948 totalled 31, which corresponds to less than 6% of the deaths in 1941. Of the 31 fatal cases, 29 were children who had never been immunized, one was an adult who

had not been immunized, and only one was a child who had been immunized. Half of the children of pre-school age and almost three-quarters of the school-children had been protected by 1948. A decrease in the number of immunizations was recorded in the second half of 1948, the number of inoculations being 38,639, compared with 73,761 in the first half-year and 46,242 in the second half of 1947.

Week Ending October 8

Notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,624, whooping-cough 908, diphtheria 84, measles 926, acute pneumonia 312, cerebro-spinal fever 37, acute poliomyelitis 340, acute polio-encephalitis 34, dysentery 290, paratyphoid fever 18, typhoid fever 18, food-poisoning 121.

Medical News

The R.C.O.G. Dinner

Princess Elizabeth and the Duke of Edinburgh were the principal guests at the dinner of the Royal College of Obstetricians and Gynaecologists held at the Dorchester on October 12, when the president, Sir William Gilliatt, was in the chair. In proposing the toast of the College, the Duke of Edinburgh said he was doing this on behalf of his wife as well as on behalf of himself. The College, he said, had been largely instrumental in reducing infantile and maternal mortality. It was, he said, the first to be "a Commonwealth college." He congratulated the president, Sir William Gilliatt, on looking after its affairs for the last three years: "If he has looked after them in the same capable way that he has looked after my affairs I am not surprised your College has flourished." In response Sir William Gilliatt voiced what was in the mind of everyone in saying that they were proud and delighted that their Royal Highnesses had graced them with their presence. He hoped they felt that the College had made a significant contribution to the community in looking after the welfare of mothers and infants. His fervent hope was that the College would press for the continuous improvement in medical practice of all kinds. Sir William then thanked the officers and all those on the council and committees for their good work. In greeting Professor Hilda Lloyd as his successor he observed that they were the first Royal College to elect a woman as president. Mr. J. A. Stallworthy in a highly felicitous speech proposed the health of the guests. Sir Bennett Hance and Mr. Geoffrey Keynes suitably replied.

Postgraduate Travelling Fellowships

The British Postgraduate Medical Federation (University of London) is offering a limited number of travelling fellowships, tenable for one year, to registered medical practitioners who are training as specialists in one of the preclinical or clinical branches of medicine or surgery at one of the medical schools or teaching hospitals of the University of London. Further information about these fellowships will be found in the advertisement columns at p. 34.

Chelsea Clinical Society

The first dinner meeting of the fifty-third session was held on October 11 at the South Kensington Hotel, with the president, Dr. Maurice Bewley, in the chair. An interesting discussion on hormones was opened by Dr. P. M. F. Bishop and continued by Dr. Raymond Greene.

Road Accidents

Discussing physical disabilities and alcoholism in relation to road accidents at the Congress of the Royal Society for the Prevention of Accidents on October 5, Dr. J. A. Gorsky said that the field was comparatively unexplored. There was an urgent need for further investigation into the problems of visual defects and accident proneness as causative factors in road accidents. The danger of alcohol to drivers was becoming recognized and appreciated by the responsible majority of motorists, but more needed to be done by way of propaganda and public relations. He was astonished that in the case of fatal road accidents the Ministry of Transport did not adopt the same procedure as the Ministry of Labour, which sends one of its factory inspectors to attend the coroner's inquest when there has been a fatal industrial accident. It might be necessary to make tests for driving licences more stringent. That would mean a sacrifice of freedom. Most people who thought clearly about the problem had recognized the point, but it meant an enormous change of attitude and outlook.

History of War

The lines on which the official medical histories of the last war are being prepared were described in the *Medical Journal of Australia* of June 18 (p. 818) by Mr. W. F. Mellor, secretary of the United Kingdom Official Medical History of the War. In Britain as early as March, 1941, an editorial board was set up under the chairmanship of the Rt. Hon. R. A. Butler, M.P., then President of the Board of Education, with Sir Arthur MacNalty as Editor-in-Chief. The board first met in July of the same year. Subsequently Sir Cyril Flower, Deputy Keeper of the Public Records, succeeded to the chair of the board. Similar work was started in the Commonwealth and the U.S.A. The medical history will be divided into three main sections: (1) Evolution and development of the administrative services to meet war conditions; (2) the medical aspects of the campaigns; and (3) the advances in clinical medicine and surgery. There will also be sections on medical research and statistics. A number of the histories were already in preparation when the war ended in 1945. A conference of Commonwealth medical historians to study the possibilities of collaboration was therefore held in London in January, 1946, and as a result a liaison committee was established. This committee last met at Canberra on October 3–8 and discussed in particular the campaign in the Near and Far East, as well as the progress made in those theatres in the prevention and treatment of tropical diseases.

Memorial to Dr. John Snow

A tablet commemorating Dr. John Snow's residence at 18, Sackville Street, London, W.1, was affixed to this house on October 18. The tablet is inscribed "John Snow (1813–1858), physician and specialist anaesthetist, who discovered that cholera is water-borne, lived here." It was John Snow who administered chloroform to H.M. Queen Victoria on April 7, 1853, at the birth of the Prince Leopold. His work on cholera overshadowed his fame as a pioneer anaesthetist.

Exploring Norway

The British Schools Exploring Society is arranging an expedition to Northern Norway from August 2 to September 15, 1950, and invites applications for the posts of honorary physician and honorary surgeon. The cost to each member of the party will be £110, plus £12 for personal equipment. Applicants should write as soon as possible to the assistant secretary of the society, c/o Royal Empire Society, Northumberland Avenue, London, W.C.2, suggesting a day when they could come to London for an interview.

Princess Tsahai Memorial Hospital

A bazaar will be held at the Kingsway Hall, London, W.C.2, on December 1 from 3 p.m. to 7 p.m. and on December 2 from 11 a.m. in aid of the Princess Tsahai Memorial Hospital. Funds are still urgently needed to complete the hospital, and cheques and postal orders will be gratefully received by the honorary treasurers, Lord Horder and Lord Amulree, c/o Messrs. Gould and Prideaux, 88, Bishopsgate, London, E.C.2. Gifts for the bazaar and offers to help should be sent to the honorary secretary, Miss E. Sylvia Pankhurst, 3, Charteris Road, Woodford, Essex.

Carnegie United Kingdom Trust

Mr. J. Murray Black, surgeon to Dunfermline and West Fife Hospital, was elected a life trustee of the Carnegie United Kingdom Trust in March this year.

Milk Foods

Proprietary infant milk foods and National Dried Milk are now available as an alternative to liquid milk for children up to 2 years of age instead of 1 year. Anyone wanting to obtain permission to buy these preparations for a child between the ages of 1 and 2 should take or send the child's ration book to the local food office.

COMING EVENTS

Honyman Gillespie Lectures

A series of Honyman Gillespie Lectures has been arranged in association with the Edinburgh postgraduate courses to take place during the autumn term in the anatomy theatre, University New Buildings, Teviot Place, Edinburgh, on Thursdays, at 5 p.m. The first lecture on "Regional Ileitis" was delivered by Mr. James S. Jeffrey on October 20, and the series will end on December 1. Details will be published under "Societies and Lectures" in the *Journal* week by week. The lectures are open to all graduates and senior students.

Torquay Medical Society

The following lectures will be given at the meetings of the Torquay and District Medical Society at Torbay Hospital: "Common Gynaecological Lesions and their Diagnosis," by Mr. H. J. Drew Smythe, October 27 at 8.30 p.m.; "Headache," by Dr. Anthony Feiling, November 24 at 8.30 p.m.; "The Coroner and the Modern Medical Profession," by Mr. Bentley Purchase, January 12, 1950, at 8.30 p.m.; "Modern Clinical Endocrinology," by Dr. S. L. Simpson, February 9, 1950, at 8.30 p.m.; "Some Recent Advances in Paediatrics" by Dr. Wilfred Sheldon, March 9, 1950, at 8.30 p.m.; and "Diseases of the Rectum and Anus and their Treatment," by Mr. R. Marnham, March 23, 1950, at 8.30 p.m.

University College Hospital Medical School

The annual dinner of past and present students (men and women) of University College Hospital Medical School will be held at Savoy Hotel, Strand, W.C., on Friday, October 28, at 7.30 for 8 p.m., when the chair will be taken by Mr. John B. Hunter. Applications for tickets (£1 7s. 6d. each), accompanied by remittance, should be made to the dinner secretary, University College Hospital Medical School, University Street, London, W.C.1. On Thursday and Friday, October 27 and 28, there will be lectures and demonstrations for old students at the medical school from 10.30 a.m. to 5 p.m., and on Friday, October 28, at 5 p.m. the annual general meeting of the Old Students' Club will be held in the Medical Society's rooms in the Medical School.

Royal Dental Hospital of London

A dinner of past and present students of the Royal Dental Hospital of London will be held at the Savoy Hotel, London, W.C., on Saturday, October 29, at 7 for 7.30 p.m., when Professor E. C. Sprawson will preside. The annual clinical "At Home" will be held at the hospital, 32, Leicester Square, W.C., at 3 p.m. the same day, when cases of clinical interest illustrating the scope of the work undertaken by the hospital will be shown and the various departments of the hospital and school will be open for inspection. At 12.30 p.m. Dr. Lilian Lindsay will formally open the Stobie Memorial Library.

Organic Nervous Disease

The Committee on the Welfare of the Disabled of the Scottish Council of Social Service has arranged for a conference to be held on "The Disability of Organic Nervous Disease" at the Lesser City Hall, Perth, on November 4–5. There will be delegates representing the education, health, and welfare committees of local authorities and of voluntary organizations. The speakers include Dr. G. W. Ireland, on "The Problems of Nervous Disease from the Point of View of a General Practitioner"; Dr. John B. Gaylor, on "The Nature of Epilepsy"; Dr. J. Romanes Davidson, on "The Function of the Epileptic Colony"; and Mr. Joseph Schorstein, on "Head Injuries." Further information may be obtained from the Scottish Council of Social Service, 10, Alva Street, Edinburgh.

Lighting in Hospitals

A paper on "Specialized and General Lighting in Hospitals" by Mr. M. W. Pierce and Mr. D. J. Reed will be read at a meeting of the Illuminating Engineering Society on November 8 at 6 p.m. The meeting starts at 5.15 p.m. and will be held at the Lighting Service Bureau, 2, Savoy Hill, London, W.C.2. Particulars may be obtained from the society at 32, Victoria Street, London, S.W.1.

SOCIETIES AND LECTURES

Friday

British Institute of Radiology.—At Reid-Knox Hall, 32, Welbeck Street, London, W., October 21, 5 p.m., Meeting of medical members; 6.30 p.m., "*Standardization of Radioactive Isotopes*." Speakers: L. H. Gray, Ph.D., J. L. Putman, M.A., and W. K. Sinclair, M.Sc.

Maida Vale Hospital for Nervous Diseases Medical School, Maida Vale, London, W.—October 21, 5 p.m., clinical demonstration by Dr. A. Feiling.

Medical Women's Federation.—At City Hall, Cardiff, October 21, 3 p.m., annual general meeting; 8.30 p.m., at National Museum of Wales, reception by Cardiff Division of B.M.A.

Middlesex County Medical Society.—At Hillingdon Hospital, Uxbridge, October 21, 3 p.m., demonstration of radiographs and pathological specimens; 3.15 p.m., business meeting, followed by paper on "*Respiratory Patterns during Surgery and Anaesthesia*," by Dr. H. J. V. Morton; 5 p.m., "*Diagnosis in Cases of Jaundice*," by Dr. A. R. Harrison. A discussion will follow each paper.

Monday

Medical Society of London, 11, Chandos Street, Cavendish Square, London, W.—October 24, 8.30 p.m., Discussion: "*Deafness*," to be introduced by Messrs. T. E. Cawthorne and I. G. Robin.

University College, Gower Street, London, W.C.—October 24, 4.45 p.m., "*Technique and Applications of Tissue Culture*," by Dr. Charity Waymouth.

Tuesday

Barrow and Furness Clinical Society.—At Orthopaedic Clinic, North Lonsdale Hospital, October 25, 8 p.m., first meeting of season.

Bristol University.—At Large Physics Lecture Theatre (Royal Fort), October 25, 8.15 p.m., "*The Use of Tracer Elements in Biology and Medicine*," 38th Long Fox Memorial Lecture by Professor J. E. Harris.

Edinburgh Postgraduate Board for Medicine.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, October 25, 5 p.m., "*New Orientations in Epilepsy*," by Dr. Denis J. Williams.

Eugenics Society.—At 26, Portland Place, London, W., October 25, 5 p.m., "*Intelligence and Fertility: An Investigation of Scottish Children*," by Sir Godfrey Thomson, D.C.L., Ph.D., D.Sc. All interested are invited to attend.

Institute of Dermatology, 5, Lisle Street, Leicester Square, London, W.C.—October 25, 5 p.m., "*Histopathology of the Skin*," by Dr. I. Muende.

Institute of Obstetrics and Gynaecology.—At Postgraduate Medical School of London, Ducane Road, W., October 25, (1) 2 p.m., "*The Problems of Mammary Carcinoma in Pregnancy*," by Mr. A. Lawrence Abel; (2) 3 p.m., "*Anaemia in Pregnancy*," by Professor L. S. P. Davidson.

London University.—At St. Mary's Hospital Medical School, Norfolk Place, Paddington, London, W., October 25, 5 p.m., "*Recent Studies in the Physiology and Pharmacology of the Cerebral Circulation*," by Professor C. F. Schmidt (University of Pennsylvania).

Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.—October 25, 5 p.m., "*The Development of the Mammary Gland*," Arris and Gale Lecture by Mr. E. S. R. Hughes.

Wednesday

Glasgow University: Department of Ophthalmology.—October 26, 8 p.m., "*Gyrate Atrophy of the Choroid*," by Dr. A. Wright Thomson.

Institute of Obstetrics and Gynaecology.—At Chelsea Hospital for Women, Dovehouse Street, London, S.W., October 26, (1) 11 a.m., "*Vaginal Hysterectomy, Indications and Technique*," by Mr. C. M. Gwillim: (2) 12 noon, "*Oestrogens*," by Professor E. C. Dodds, F.R.S.

Royal Institute of Public Health and Hygiene, 28, Portland Place, London, W.—October 26, 3.30 p.m., "*Some Popular Fallacies Regarding Human Nutrition*," by Dr. H. E. Magee.

Royal Sanitary Institute, 90, Buckingham Palace Road, London, S.W.—October 26, 2.30 p.m., "*The Common Cold*," discussion to be opened by Dr. W. H. Bradley (Ministry of Health).

Social Psychotherapy Centre, 7, Fellows Road, London, N.W.—October 26, 5 p.m., "*The History of Social Psychiatry and Group Psychotherapy and the Principles of Social Psychiatry*," by Dr. Joshua Bierer.

Society of Chemical Industry.—Joint meeting of Nutrition Panel and Agriculture Group at Chemical Society's rooms, Burlington House, Piccadilly, London, W., October 26, 6.15 p.m., "*Genetic Factors Affecting the Nutritional Value of Animal Products*," by Dr. J. Hammond; "*Genetic Factors Affecting the Nutritional Value of Crops*," by Mr. R. H. Richens.

Thursday

Honyman Gillespie Lecture.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, October 27, 5 p.m., "*Diastole*," by Dr. Bruce Williamson.

Institute of Urology.—At Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C., October 27, 5 p.m., "*Bone Syphilis*," by Mr. A. E. W. McLachlan.

Medico-Legal Society.—At 26, Portland Place, London, W., October 27, 8.15 p.m., "*The Use of Scientific Research in Medico-legal Practice*," Presidential address by Dame Louise McIlroy.

St. George's Hospital Medical School, Hyde Park Corner, London, S.W.—October 27, 4.30 p.m., lecture-demonstration: "*Psychiatry*," by Dr. D. Curran

Torquay and District Medical Society.—At Torbay Hospital, October 27, 8.30 p.m., "*Common Gynaecological Lesions and their Diagnosis*," by Mr. H. J. Drew Smythe.

Friday

Kent and Canterbury Hospital, Canterbury.—October 28, 8 p.m., clinical meeting.

London University.—At Westminster Medical School (Meyerstein Lecture Theatre), Horseferry Road, London, S.W., October 28, 5.30 p.m., "*The Indispensability of Biologically Labile Methyl Groups in the Diet and Transmethylation*," by Professor V. du Vigneaud (Cornell University Medical College).

Maida Vale Hospital for Nervous Diseases Medical School, Maida Vale, London, W.—October 28, 5 p.m., clinical demonstration by Dr. S. Nevin.

Medical Society for the Study of Venereal Diseases, 11, Chandos Street, London, W.—October 28, 8 p.m., "*Is Treatment Before Diagnosis on Suspicion of Venereal Disease Advantageous to (a) the Patient, (b) the Public Health?*" discussion to be opened by Colonel L. W. Harrison.

Royal Institute of Philosophy, 14, Gordon Square, London, W.C.—October 28, 5.15 p.m., "*Russell's Neutral Monism*," by Professor H. H. Price.

Royal Medical Society, 7, Melbourne Place, Edinburgh.—October 28, 8 p.m., "*The Dawn of Tropical Medicine (The Life and Work of Sir Patrick Manson)*," by Sir Philip Manson-Bahr.

University College, Gower Street, London, W.C.—October 28, 5.15 p.m., "*Transmission of Excitation in Nerve and Muscle*," by Dr. Bernhard Katz.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

John.—On October 6, 1949, at 2, Chessel Avenue, Southampton, to Gene (née Sinton) and Dr. Alan Oakley John, a sister for Marilyn and Elisabeth—Alison Ruth.

Kerr.—On October 9, 1949, at Aylesbury, to Mary (née Talbot), wife of J. G. Kerr, M.Ch.(Orth.), a son.

MARRIAGES

Critchley—Watson.—On October 1, 1949, at St. Paul's Church, Birkenshaw, Yorks, James Michael Allis Critchley, M.B., Ch.B., to Isobel Vernon Watson, M.B., Ch.B.

Davies—Stuart.—On September 13, 1949, at Blackfriars Church, Glasgow, David M. Davies, M.B., B.Ch., to Marie Stuart.

DEATHS

Inglis.—On October 12, 1949, at Falkirk Royal Infirmary, James Charles Inglis, M.B., Ch.B.

James.—On October 13, 1949, at the National Hospital, Queen Square, London, W.C., Richard Gostwycke James, O.B.E., M.R.C.S., L.R.C.P., of Kingham, Norwich, Norfolk.

Kaye.—On October 2, 1949, at Boscombe Hospital, Ernest George Kaye, M.B., B.S., of 40, Princess Road, Bournemouth West, aged 76.

Kyle.—On October 8, 1949, at St. George's Hospital, James Kyle, M.R.C.S., L.R.C.P., Air Commodore, R.A.F. Medical Branch, Ret., of Brendon, Wendover, Bucks.

La Frenais.—On October 2, 1949, Joseph Everett La Frenais, L.R.C.P.&S.Ed., L.R.F.P.S., of Tower House, Runcorn, Cheshire.

Lanyon.—On October 4, 1949, at Penzance, Edgar Temple Lanyon, M.R.C.S., L.R.C.P., of 49, Ullet Road, Liverpool.

Lewis.—On October 3, 1949, suddenly, at Great Ormond Street, London, W.C., Jonathan Nicholas Lewis, aged 1 year 6 months, very dear son of Drs. Charles and Evelyn Lewis, of 28, Michelham Gardens, Twickenham, Middlesex.

MacInnes.—On October 9, 1949, at Cairn Villa, Broadford, Skye, Alexander MacInnes, M.B., Ch.B.

Masson.—On October 14, 1949, at 33, Kaimes Road, Corstorphine, Edinburgh, James Masson, M.B., Ch.B., F.R.C.S.Ed., Lieutenant-Colonel I.M.S., Ret.

Milne.—On September 29, 1949, at Aldeburgh, Suffolk, Robert Milne, M.S., F.R.C.S., Surgeon Rear-Admiral R.N., of 75, Portland Place, London, W.

Raban.—On October 2, 1949, at Bristol General Hospital, John Pridmore Raban, M.R.C.S., L.R.C.P., D.M.R.E.

Wilkes.—On October 8, 1949, at Folkestone, Ernest Alfred Freear Wilkes, M.R.C.S., L.R.C.P., D.P.H., of 2, Clare Lawn Avenue, East Sheen, London, S.W.

Wilson.—On October 6, 1949, at 35, Park Place, Elie, Fife, John Johnstone Wilson, M.D., F.R.C.P.Ed., formerly of Anstruther, Fife, aged 81.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Copra Bug

Q.—*From time to time I am called upon to treat dockers suffering from alleged bites by an insect known as the "copra bug," which infests cargoes of copra. I should be glad of information about the nature of this insect, and of advice about prophylactic measures. The best solution would be treatment of the cargo with an insecticide which would not impair the edibility of the oil subsequently expressed from the copra, but, failing this, is there any local application which could be used on the dockers' skin?*

A.—The "copra bug" is a species of mite, *Tyrophagus castellani*. This mite occurs fairly commonly among stored food with a relatively high fat and protein content, such as linseed, dried egg, nuts, cheese, herring meal, and copra. Skin irritation is caused to people handling infested foodstuffs, possibly by the excretory products as well as by the mites themselves, for material containing large numbers of dead mites is said to cause the same symptoms. The easiest way to deal with complaints of irritation from this mite is to introduce a repellent to be rubbed on the skin of persons coming in contact with it. Undiluted dimethyl phthalate can be used, or a preparation containing 30 to 40% of it; several such preparations are available. A small quantity of the repellent should be rubbed over the skin of the hands, arms, etc., of the workmen each morning.

Cancer of Cervix Uteri

Q.—*Is it ever necessary or advisable to repeat treatment with radium for cancer of the cervix? A woman of 36, a multipara, with a carcinoma proved at biopsy, has been given three radium exposures of 1,800, 2,000, and 1,875 units (total 5,675 units) followed by 12 deep x-ray irradiations at one to two days' intervals. The bleeding stopped after the first exposure to radium. Severe excruciating pain radiating down the left thigh and the coccygeal region occurred after the second radium exposure and persisted till a month ago, when an ulcer covered by offensive slough was detected at the site of the cancer. The surrounding area was hard and tender. A course of penicillin injections was then started, and this relieved the pain. Every evening there is tingling or mild pain in the lower abdomen or left thigh. The ulcer is clean but not healed, and the surrounding area is somewhat hard. Local penicillin ointment is being continued. There is no glandular enlargement or metastasis. Could you advise me on the next steps to be taken? What is the latest treatment of this type of cancer?*

A.—This question is in three parts. The first is a general question on the need for or advisability of repeated treatment with radium for cancer of the cervix. Only in a very few cases of cancer of the cervix specially selected on their merits would irradiation with radium be justifiable. In general, subsequent irradiation of the cervix following a full course of irradiation by radium or by radium and *x* rays will do nothing but harm.

The second part of the question is concerned with an individual patient. The information given does not include details of the time between the radium exposures or the size, arrangement, or dosage of the *x*-ray fields or the quality of the *x*-ray radiation used. If the treatment was of the type frequently used, it would seem that the initial course was reasonably adequate or even possibly a little excessive. It appears likely that there is some infection in the left pelvis, the situation of the pain suggesting that this might have been in a lymph node in the pelvic wall. The presence of an ulcer at the site of the cancer does not necessarily indicate a recurrence; this might be a radio-necrotic ulcer to which infection could have

been a contributory cause. It would be advisable to make sure that the ulcer is free from Gram-negative organisms before using penicillin ointment. In spite of the absence on examination of evidence of glandular enlargement or metastasis, the pain of which the patient complains suggests some irritation of the upper lumbar nerve distribution on the left side. As regards treatment, the following is suggested. Biopsy of the ulcer should be performed and local treatment with sulphonamides and penicillin continued. If the ulcer is malignant, hysterectomy should be carried out if possible, at which the glands can be inspected and localized; these might subsequently be irradiated. A Wertheim hysterectomy in skilled hands would be preferable. If hysterectomy is contraindicated, then local treatment by diathermy coagulation should be given, followed by local removal of the cervix if healing does not seem to be well advanced in two months. If the ulcer is benign, local treatment with sulphonamides and penicillin supplemented by hypertonic saline douches should be continued. Coagulation diathermy of the ulcer could be tried, but not until at least three months have elapsed.

To the third part of the question—What is the latest treatment for this type of cancer?—the answer is, Very extensive surgery, according to the clinical stage, or radium and *x*-ray treatment combined; though different practitioners would probably give different answers. The best published results are from the Marie Curie Hospital, London, and the Fondation Curie Hospital, Paris, both radiotherapeutic institutions.

Suspected Food-poisoning

Q.—*During the summer there have been numerous isolated attacks of sickness and diarrhoea which have cleared up in a few days with simple treatment. These attacks are probably due to something the patients have eaten. Should these cases be notified and, if so, under what heading?*

A.—If it is suspected that cases of sickness and diarrhoea are due to food inherently non-poisonous but to which has been added, or in which has developed, a toxic substance (chemical or bacterial) or a growth of pathogenic bacteria, such cases should be notified as food-poisoning under Section 17 of the Food and Drugs Act, 1938. The main purpose of this section of the Act is to ensure that the local medical officer of health is informed of outbreaks of illness occurring in his district and believed to have been caused by food. The Act did not give any definition of the term "food-poisoning," but the matter is dealt with in the Ministry of Health Memorandum on Food Poisoning, No. 188/Med. (revised 1949), from which it is clear that cases in which food causes an infectious disease otherwise statutorily notifiable as such—for example, typhoid fever, scarlet fever, and dysentery—should not be notified as food-poisoning. It is evident, however, that there would be no reflection on a doctor who, on clinical grounds, notifies as food-poisoning a case in which the final diagnosis after investigation proves to be dysentery. The medical officer of health can, with the consent of the doctor concerned, correct such provisional notifications in the quarterly return made to the Registrar-General. Illness due to individual idiosyncrasy to certain foods—that is, to allergy or hypersensitivity—and to the consumption of foods inherently poisonous—for example, toxic fungi mistaken for mushrooms—should not be notified as food-poisoning.

Interpretation of Dreams

Q.—*Can you explain why the manifest dream is sometimes, if not always, so fantastically different from the thoughts or feelings which have given rise to it? I was woken by such a dream last night. Associations came easily and soon the underlying causes seemed clear. But for a long time I lay awake wondering why it had been necessary to wrap them up so elaborately.*

A.—There are several theories of the interpretation of dreams, but in the writer's opinion the dream is always the product of an unresolved problem, which, because we cannot solve it, we repress so that it becomes unconscious (which, indeed, is the next best thing to do if we cannot solve it, so that we may get on with the business of life). But the problem nevertheless remains, and refuses to be repressed, being insistent that its claims should be attended to. Therefore what we refuse to acknowledge in waking life emerges as a dream, which forces us to face a problem we are refusing to face. But also because we refuse to allow the problem in consciousness it must appear in disguised forms. Sometimes it does this by symbols which are less direct than the unpleasant facts themselves. Sometimes we draw upon earlier experiences of the same nature, having the same emotion, exemplifying the same type of experience, or illustrative of the same problem. So bits of past experiences, apparently irrelevant and illogical, but always associated with the problem, appear in the dreams. In other cases the problem is put in a more acceptable light, such as when feelings of rage appear as righteous indignation, or feelings of humiliation are transformed into humiliating others. Indeed, it does not seem to matter a great deal how the problem or emotion comes out so long as it is released and the unpleasant problem is brought to mind. Freud has dealt with many of the causes of such "dream distortion" in his *Interpretation of Dreams*.

In brief, distortion is due to our refusal to face the problem as such, so that other relevant material illustrative of the problem or in some way associated with it is drawn upon to serve the purpose of forcing its attention on a reluctant mind for solution. It is all these symbols, scraps of experiences, transformations, and substitutions which give to the dream its bizarre nature; and it is only by investigating each item that we can fit them, like a jigsaw, into a reasonable pattern.

NOTES AND COMMENTS

Antiseptics for Minor Dressings.—Mr. John Roberts (Bangor, Caernarvonshire) writes: I would like to support Dr. Rupert Palmer (October 1, p. 768) in his spirited defence of mercury perchloride. Without doubt it is one of our most valuable, efficient, and inexpensive antiseptics, with the great advantage of being lethal to the majority of pathogenic organisms, which cannot be claimed for some of the modern and selective biochemical products. There are theoretical disadvantages to this chemical in that it is highly toxic parenterally and it coagulates tissue albumins, etc., but these objections come from laboratory workers and others out of touch with daily clinical work in which the drug is used as a surface application. It may be that it has come under suspicion because of occasional harmful results from mercurial diuretics or from occasional cases of chronic poisoning in pink disease and in finger-print workers using the material habitually, but this is no reason for condemning such a useful and potent antiseptic.

A 1 in 4,000 solution of mercury perchloride in warm water is invaluable as an irrigating lotion in cases of middle-ear suppuration, and if the tympanic membrane is intact a 1 in 2,000 solution can safely and most efficiently be used for external otitis (including the fungoid infections). I have used the weaker solution with much success for washing out the odd case of persistently dirty maxillary antrum (a few with gross fungus infection), but only through an antrostomy opening. Idiosyncrasy has been extremely rare in my experience, and this is in agreement with Dr. Palmer's remarks.

For surgery or hospital use mercury perchloride is available in the small, readily soluble 1.75-gr. (50-mg.) tablet, coloured blue, and one of these dissolved in 4 oz. (114 ml.) of water gives a 1 in 1,000 solution. One tablet in 16 oz. (454 ml.) of warm water is correct for middle-ear suppuration. These tablets are of course intensely poisonous by mouth, and the 1 in 1,000 solution (coloured blue) for appropriate dilution should be used for dispensing, with all due precautions. I am aware of the claims of the new organic mercurials (phenyl mercuric acetate, nitrate, chloride, etc.), but so far I have been quite satisfied with the older chemical.

All communications with regard to editorial business should be addressed to The Editor, British Medical Journal, B.M.A. House, Tavistock Square, London, W.C.1. Telephone: Euston 2111. Telegrams: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS. if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Manager, B.M.A. House, Tavistock Square, London, W.C.1 (hours 9 a.m. to 5 p.m.). Telephone: Euston 2111. Telegrams: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. Telephone: Euston 2111. Telegrams: *Medisecra, Westcent, London.*

B.M.A. Scottish Office: 7, Drumsheugh Gardens, Edinburgh.